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CORONARY ARTERIOSCLEROSIS, CORONARY ANASTOMOSES AND MYOCARDIAL INFARCTION

A Clinicopathologic Study Based on an Injection Method

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AND
E. F. GEEVER, M.D.
DENVER

IN 1938 Schlesinger [1] described a method for the postmortem study of changes in the coronary arteries which has opened a new field in the study of diseases of the coronary artery. At the University of Colorado School of Medicine 166 hearts have been studied thus far by the Schlesinger method. With this technic the right and left coronary arteries of the unembalmed heart are cannulated, and a mixture of agar and a lead salt is injected into the arteries. The agar is coagulated by cooling the heart, which is then unrolled by a series of incisions so that the coronary arteries are flattened out into one plane. The lead salt in the injection mixture is opaque to roentgen rays, and a roentgenogram is taken of the heart. An example of the roentgenogram which is obtained is shown in figure 1 *I*, in which the various parts of the heart are indicated. The mass which is injected into the right coronary artery is colored red with carbolfuchsin, and that in the left coronary artery is colored blue with methylene blue. After the roentgenogram has been taken the arteries are opened with fine scissors, and the color of the injected mass and the state of the arterial wall are indicated on a semitransparent paper copy of the roentgenogram. This is easily determined, because the arteries are filled with the mass and the arterial walls are colored by the dye. A coarse reproduction of the roentgenogram in figure 1 *I* with the colors indicated is illustrated in the sketch, figure 1 *II*. Normally, no mixing of the mass injected into the two arteries occurs. This was proved in a number of hearts in which one or the other of the arteries was not injected because of faulty technic; the mass filled

From the Departments of Medicine and Pathology, University of Colorado School of Medicine.

Dr. J. J. Waring, Professor of Medicine at the University of Colorado School of Medicine, made this study possible and gave many valuable suggestions.

1. Schlesinger, M. J.: Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, Am. Heart J. **15**:528 (May) 1938.

only the artery injected. It did not extend in retrograde fashion into the other vessel.

The injected mass always penetrates to arterioles 40 microns in diameter and reaches about 50 per cent of the vessels 20 microns in diameter.[1] The normal failure of the colors to mix indicates that, in the normal heart at least, there are no anastomotic vessels greater than 20 to 40 microns in diameter. If anastomotic vessels greater than 20 microns in diameter are present mixing of the masses and of their colors occurs. Where such mixing occurs the resultant mass is purple.

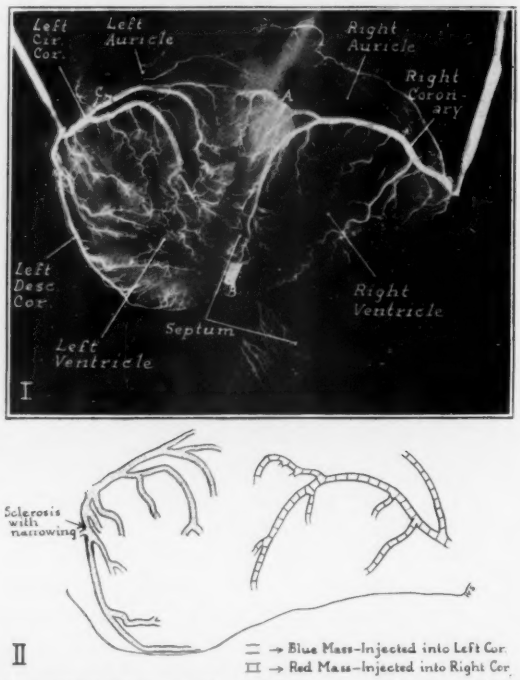

Fig. 1.—*I*, roentgenogram of the unrolled heart with the injected coronary arteries and anatomic landmarks labeled. *A* and *B* indicate the posterior cardiac wall at its junction with the interventricular septum. Small artefacts in the left circumflex artery are indicated at *C*. The arterial pattern is the balanced type. *II*, sketch reproducing grossly the main features of the roentgenogram in *I* and indicating the distribution of colors in a normal heart.

RESULTS

Except for less than a half-dozen hearts which were brought to us because they were expected to show changes, our series of 166 hearts was unselected and included a wide range of pathologic conditions. Thus in many cases the heart was normal, and the cause of death was unrelated to it. Eighteen hearts revealed coronary occlusions; of this

group 7 specimens showed more than one occlusion. In 14 hearts the occlusions were due to acute or subacute coronary thrombosis. Thirty-six hearts revealed interarterial anastomoses. The ages of the patients whose hearts were studied post mortem had varied from less than 1 year to 90 years, and the number of patients in each decade is listed in the accompanying table.

Results of Postmortem Study of Changes in Coronary Arteries

Age Group, Yr.	Number in Each Group	Coronary Pattern			Coronary Occlusions				Myocardial Infarction Without Occlusion	Anastomosis	
		Right	Balanced	Left	All Types	Multiple	Without Infarction	With Infarction		All Types	Without Occlusion
<10	2	2	0	0	0	0	0	0	0	0	0
11-20	5	1	4	0	0	0	0	0	0	1	1
21-30	15	7	5	3	0	0	0	0	0	0	0
31-40	8	4	3	1	1	1	1	0	0	1	0
41-50	23	13	7	3	3	2	1	2	0	6	3
51-60	42	20	17	5	6	1	2	4	1	11	6
61-70	33	19	10	4	3	2	1	2	0	7	5
71-80	27	13	11	3	3	1	0	3	1	8	6
81-90	11	7	2	2	2	0	0	2	0	2	0
Total	166	86	59	21	18	7	5	13	2	36	21

Arterial Patterns.—Examination of the pattern of the coronary arteries showed pronounced variation. However, three main types as described by Schlesinger [2] were found. Figure 1 *I* illustrates the balanced pattern of coronary circulation. In it the left coronary artery through its anterior descending and circumflex branches supplies the left ventricle and the anterior half of the interventricular septum. The right coronary artery supplies the right ventricle and provides the branch which goes down the posterior interventricular sulcus and supplies the posterior half of the septum. Figure 2 *I* shows a preponderance of the right coronary artery. The right coronary artery supplies the area described above and, in addition, a portion of the left ventricle. Preponderance of the left coronary artery is shown in figure 2 *II*. The left coronary artery furnishes the branch which goes down the posterior interventricular sulcus and supplies the posterior half of the septum. In our series we found the right preponderant pattern in 52 per cent of the cases, the balanced pattern in 35 per cent and the left preponderant pattern in 13 per cent. However, separation between types was not sharp, and various gradations were seen. On the basis of a study correlating coronary artery pattern with infarct formation and healing, Schlesinger [2] decided that hearts with preponderance of the left coronary artery suffer most from the effects of coronary arteriosclerosis, hearts with balanced blood supply suffer least and hearts with a preponderance

2. Schlesinger, M. J.: Relation of Anatomic Pattern to Pathologic Conditions of the Coronary Arteries, Arch. Path. **30**:403 (July) 1940.

of the right coronary artery are intermediate in their response. The number of cases on which his conclusions were based seems inadequate. An analysis of the cases in this series does not support his conclusions, but in our series, again, there are too few cases. A much larger series will have to be analyzed before any decision can be reached.

Anastomoses Without Occlusion.—As has been said, mixing of the masses injected in the two arteries normally does not occur. This is

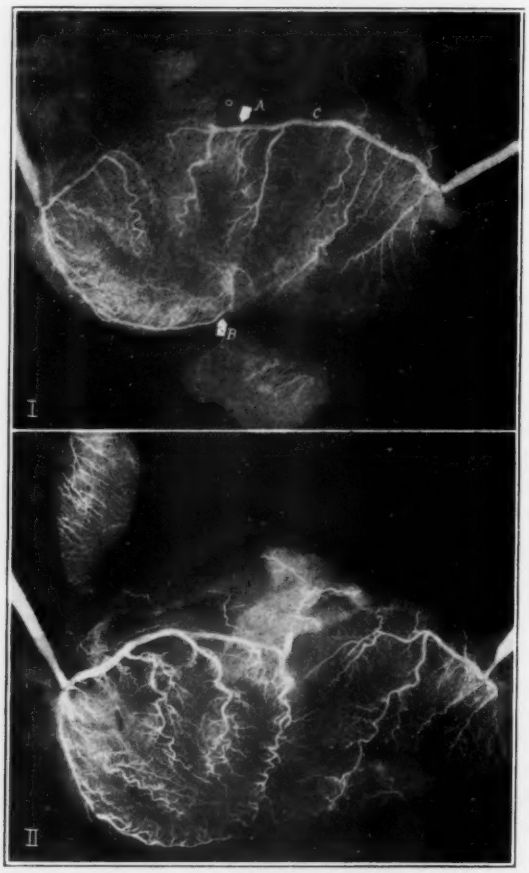

Fig. 2.—Roentgenograms illustrating the pattern of coronary artery preponderance. *I*, the right coronary artery supplies all the right ventricle, furnishes the descending artery on the posterior half of the interventricular septum and also supplies a portion of the left ventricle. *A* and *B*, the posterior cardiac wall at its junction with the interventricular septum. *C*, a small artefact. *II*, the left coronary artery supplies all of the left ventricle and furnishes the descending artery which supplies the posterior half of the interventricular septum.

true even in the hearts of persons of advanced age, if coronary sclerosis is minimal or moderate in degree. If, however, the coronary arteries become extremely sclerotic and narrowing of the lumen occurs, anastomoses may develop. Figure 3 *I* shows the sketch obtained of the injected heart of a 74 year old man who had severe bronchiectasis for fifteen years prior to his death. The onset of his disease had followed the aspiration of a chicken bone, and at autopsy a bone was found in one of the bronchi. Orthopnea had developed four weeks before his admission to the hospital, and severe dyspnea two days before his admission. He had bronchopneumonia and died shortly after entering the hospital. The heart weighed 320 Gm. and was grossly not remarkable. Owing to arteriosclerotic changes, the branches of the left coronary artery near their origin were decidedly narrowed. When these branches were opened it was found that the mass was colored not blue but purple—indicating that there had been an admixture of the red and blue masses. Anastomotic channels had formed, so that the mass (and blood) went from the right coronary artery into the left.

In figure 3 *II* the formation of anastomoses is even more definite. This is the heart of a 62 year old man who had silicosis and chronic nephritis and died of bronchopneumonia. The heart was enlarged (556 Gm.) and showed some hypertrophy of both ventricles. Microscopically there was some diffuse fibrosis. No occlusions were present, but under the stimulus of a narrowing of the arterial lumen due to arteriosclerosis, anastomoses had formed which helped to supply the left ventricle with blood. Anastomoses without occlusions were found in 21 hearts.

Occlusion Without Infarction.—It is comparatively easy, then, to proceed to the next step, the heart in which a coronary artery becomes entirely occluded without the occurrence of myocardial infarction. Figure 4 shows the roentgenogram and the sketch of the heart of a 67 year old woman who had had severe and long-standing myxedema, untreated at the time of death. She was admitted to the hospital with a fracture of the pelvis. Her heart was enlarged and she had hypertension. She died suddenly five days after admission. The heart weighed 460 Gm. and showed many interesting features, including aneurysmal dilatations of the coronary arteries—well shown in figure 4 *I*. Complete occlusion of the anterior descending coronary artery was caused by an old thrombus. The circulation beyond this was maintained by the left circumflex and right coronary arteries. No gross evidence of infarction was found; microscopically there was some scattered fibrosis but nothing which could be recognized as an infarct.

Figure 5 shows the roentgenogram and the sketch of the heart of a 39 year old man who had pulmonary and genital tuberculosis and at the time of his death had a pneumothorax on the right side. There was

nothing in his history to suggest cardiac disease, unless his complaint of epigastric pain after eating for several months prior to his death is so considered. At 10 o'clock one morning he experienced severe substernal pain requiring large doses of morphine for relief. Six hours later severe tachycardia and arrhythmia of complicated origin developed, and he died sixteen hours after the onset of the acute condition. The right coronary artery showed a complete old occlusion. Circulation was maintained beyond the point of occlusion by anastomoses between the left circumflex artery and the continuation of the right coronary artery. The blood in the continuation of the right coronary artery was actually flowing in a

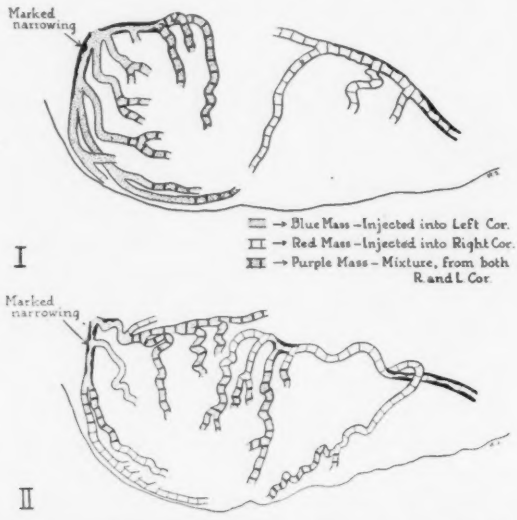
Marked narrowing
→ Blue Mass – Injected into Left Cor.
→ Red Mass – Injected into Right Cor.
→ Purple Mass – Mixture, from both R. and L. Cor.
I
Marked narrowing
II

Fig. 3.—Sketches indicating distribution of colors as a result of anastomoses. *I*, anastomoses from the right coronary artery to the left in a 74 year old man with coronary arteriosclerosis but without occlusion. *II*, anastomoses in a 62 year old man with coronary arteriosclerosis but without occlusion. Anastomoses more devious than in *I*.

retrograde direction. No infarction was present, and nothing in the history indicated when the occlusion had occurred. In the left anterior descending artery there was a fresh thrombus with complete occlusion—this had undoubtedly accounted for the acute episode starting sixteen hours before death. The artery beyond the occlusion was filled with a purplish mass indicating anastomoses between the anterior descending artery and the circumflex artery and the right coronary artery. Sixteen hours would have been time enough for an infarct to have formed, but because of the anastomoses there was no infarction; microscopically some inflammatory change was found, but no myocardial necrosis. We

had 5 cases of occlusion without infarction in our series. However, there were 5 additional cases in which infarction occurred only after multiple occlusions.

Occlusion With Infarction.—It is evident from the foregoing statements that one of the main coronary arteries may become occluded without infarct formation if the occlusion occurs slowly enough and anastomoses have time to form. On the other hand, if the occlusion occurs

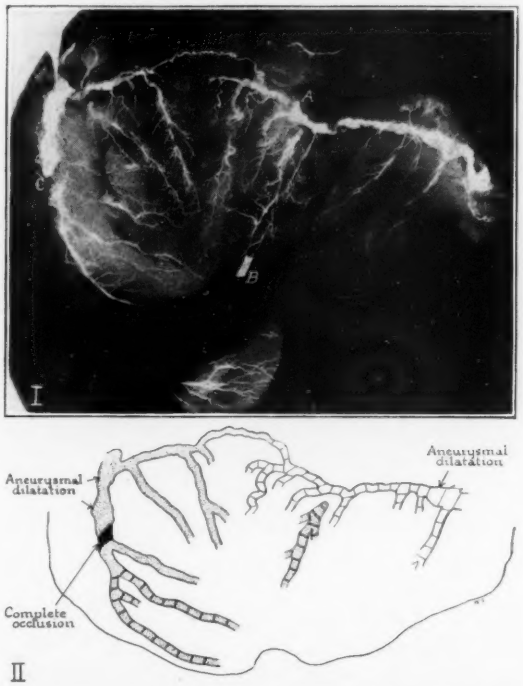

Fig. 4.—*I*, roentgenogram illustrating aneurysmal dilatations of the left anterior descending coronary artery with complete occlusion by an old thrombus at *C*. No gross myocardial infarct was present. The right coronary artery also shows aneurysmal dilatations. Breaks in the continuity of other arteries are artefacts. *A* and *B*, the posterior cardiac wall at its junction with the interventricular septum. *II*, sketch reproducing grossly the main features of the roentgenogram in *I* and indicating the distribution of colors (as in fig. 3) as a result of anastomoses. The left anterior descending artery beyond the occlusion is supplied by the left circumflex and right coronary arteries.

rapidly or, for some other unknown reason, anastomoses do not form coronary thrombosis is followed by myocardial infarction. Figure 6 shows a sketch of the injected heart of a 74 year old woman who had an acute cardiac episode a week before her sudden death. Anastomoses

were minimal, and infarction followed coronary thrombosis. There were 13 cases of occlusion with infarction in our series.

Infarction Without Occlusion.—It is well to emphasize here what must already be clear: Coronary thrombosis and myocardial infarction are not synonymous terms. This has been pointed out by Blumgart, Schlesinger and Zoll.[3] It is substantiated in figure 7, which illustrates the injected heart of a 79 year old man who entered the hospital with the

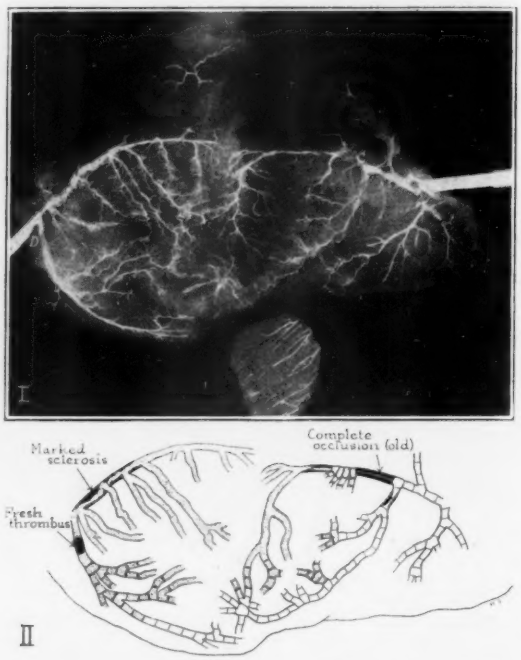

Fig. 5.—*I*, roentgenogram illustrating a complete old occlusion of the right coronary artery at *C* with a barely discernible recanalizing vessel. Fresh thrombus in the left anterior descending coronary artery at *D*. Note the numerous clearly visible anastomoses. *II*, sketch reproducing grossly the main features of the roentgenogram in *I* and indicating the distribution of colors (as in fig. 3) as a result of anastomoses.

diagnosis of senility, malnutrition and dermatitis and who died of bronchopneumonia. This heart showed no coronary occlusions and yet contained a myocardial infarct of moderate size, grossly evident and confirmed microscopically. The number of such cases reported in

3. Blumgart, H. L.; Schlesinger, M. J., and Zoll, P. M.: Angina Pectoris, Coronary Failure, and Myocardial Infarction, J. A. M. A. **116**:91 (Jan. 11) 1941.

the literature[4] is increasing. The explanation would seem to be as follows: A myocardial infarct will form if an area of muscle becomes anoxemic for a sufficiently long time. This may occur as a result of diminished blood supply following coronary thrombosis if sufficient anastomoses have not formed (figure 6). Anoxemia may also occur if the oxygen demand of the heart is increased by physical exertion, tachycardia or some other reason and the blood supply cannot be

Fig. 6.—Sketch indicating a recent thrombus in the left anterior descending coronary artery with secondary infarction. Distribution of colors (as in fig. 3) and inadequate anastomoses shown.

Fig. 7.—Roentgenogram of a heart with an infarct of moderate size indicated by crosshatching. No coronary arterial occlusion present, but there is moderate to decided sclerosis in the main stems. *A* and *B*, the posterior cardiac wall at its junction with the interventricular septum.

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4. (*a*) Gross, H., and Sternberg, W. H.: Myocardial Infarction Without Significant Lesions of the Coronary Arteries, Arch. Int. Med. **64**:249 (Aug.) 1939. (*b*) Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, J. A. M. A. **112**:1675 (April 29) 1939. (*c*) Holyoke, J. B.: Coronary Arteriosclerosis and Myocardial Infarction as Studied by an Injection Technic, Arch. Path. **39**:268 (April) 1945.

correspondingly increased because of extreme coronary narrowing due to arteriosclerosis. Anoxemia may result from a decrease in blood supply associated with anemia, shock, toxemia or tachycardia in a heart already handicapped by coronary arteriosclerosis. Experimentally, temporary coronary arterial occlusion for forty minutes will produce an infarct in the dog.[5] It is reasonable to believe that more prolonged, if milder, anoxemia also can result in infarction. In our series we had 2 cases of infarction without coronary occlusion.

Hypoplasia of the Coronary Artery.—In a comparative examination of the injected hearts in our series we observed occasional striking variations in the caliber of normal vessels. Some hearts showed uniformly hypoplastic arterial systems. Such an example is presented

Fig. 8.—Roentgenogram of heart with uniformly small coronary arteries. Compare with arteries in figure 2 *I* or 2 *II*. *A* and *B*, the posterior cardiac wall at its junction with the interventricular septum. Fresh thrombus present at *C* and old occlusion at *D*. Note the numerous clearly visible anastomoses.

in figure 8, the roentgenogram of the heart of a 45 year old man. Note the difference in caliber of the coronary arterial system as compared with that shown in figure 2 *I*—a somewhat smaller heart in a person of approximately the same age. The dangerous sequelae of arteriosclerosis, i. e. occlusions with or without thrombosis, are more likely to occur in a heart with congenitally small vessels than in one with arteries of normal caliber. This was borne out in the case illustrated by figure 8,

5. Blumgart, H. L.; Gilligan, D. R., and Schlesinger, M. J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries: II. The Production of Myocardial Infarction, Am. Heart J. **22**:374 (Sept.) 1941.

in which fatal infarction occurred. We intend to present a future report on the results of more extensive studies of hypoplasia of the coronary artery.

Coronary Arteries in Patients of Advanced Age.—The hearts of the 11 patients over 80 years of age are worthy of brief comment. Only 2 specimens of this group showed significant coronary pathologic changes: arteriosclerosis, thrombosis, infarction and anastomoses. In the remaining 9 hearts we found mild to moderate arteriosclerosis and scattered myocardial fibrosis, usually detectable only on microscopic examination.

Anomalies of the Coronary Arteries.—Of the three main stems, the left circumflex artery showed the most frequent variation. In several hearts the size and distribution of this vessel were remarkably decreased. In 1 case the left circumflex artery was absent and the area normally supplied by it was nourished by the right coronary artery. One heart had complete absence of the right coronary artery. The left circumflex branch was a long vessel which took over the function of supplying the right ventricle. It also supplied a descending branch along the posterior border of the intraventricular septum. Death in this patient was of extracardiac origin, and adequate coronary circulation could be assumed despite the anomaly.

COMMENT

The clinical implications of the facts presented warrant consideration, particularly with reference to the prognosis and therapeusis of coronary arterial disease. Each heart as its vessels become sclerotic shows a balance between the rate of narrowing of the coronary artery and the development of anastomoses. In spite of much research, it is not known what factors, other than possibly age, anoxemia, fat metabolism and mechanical wear, are involved in the rate with which arteriosclerosis occurs. It is known that the narrowing of a vessel predisposes to formation of anastomoses. Why the narrowing should predispose to anastomoses and what other factors influence their formation have not yet been determined. Some day control of the factors favoring arteriosclerosis and those favoring the formation of anastomoses may open a new field in cardiac therapeutics.

The balance between the rate of development of arteriosclerosis and the rate of formation of anastomoses will decide what will happen. If the narrowing occurs rapidly and the formation of anastomoses is slow, then thrombosis, or occlusion from any other cause, will produce an area of decidedly anoxemic cardiac muscle with a resultant infarct. The classic clinical picture of myocardial infarction then occurs: initially, severe pain, shock and collapse; later, evidence of myocardial weakness and of inflammation, such as fever, leukocytosis and elevated sedimentation rate. The electrocardiographic changes are usually diagnostic.

If the narrowing of the vessel occurs slowly and adequate anastomoses form, it is possible for thrombosis to occur with little or no evidence of myocardial involvement. The collateral circulation is so adequate that only minimal change occurs in the muscle. This may consist of a mild inflammatory reaction due to anoxemia or inflammation and microscopic focal areas of necrosis. Clinically the patient may have an attack of mild or moderately severe substernal pain which passes off in a few minutes or an hour, and he may feel somewhat "under the weather" for a few days. The entire episode may be passed off as an attack of indigestion or neuritis and may soon be forgotten. The electrocardiogram may show no changes in spite of careful and repeated search, or it may show clearly recognizable changes which last for only a few hours or days and then return to normal. The temperature, pulse rate, blood count and sedimentation rate may be slightly elevated for a short time or may remain normal. These are the cases of coronary occlusion without infarction or, at most, with microscopic focal necrosis. Death may occur during one of these attacks due to the development of cardiac standstill or an arrhythmia, i. e., ventricular tachycardia and fibrillation; but the prognosis in most cases is otherwise good.

Between these extremes, changes of intermediate character may occur. If a moderate number of anastomoses have formed, the anoxemia is of an intermediate degree and the area of necrosis is smaller than would be expected from the size of the vessel occluded. The clinical symptoms would, of course, depend on the size of the infarct.

Two important conclusions may be drawn from the foregoing statements: The first is that the longer an occlusion is delayed in a patient whose coronary arteries are becoming sclerotic, the more time anastomoses have to form and the better the chance for survival with minimal damage. In a patient, therefore, in whom one has a warning of the presence of sclerosis, say in the form of angina of effort, any measure which postpones the eventual occlusion would be of great benefit. Such measures might vary in individual cases, but a decrease in activity and administration of coronary vasodilators would certainly seem indicated. From a legal standpoint it is also true that anything which precipitates a coronary occlusion sooner than it might have occurred, has medicolegal significance, even though it may be argued that the coronary occlusion would have occurred anyway.

The second point is that rest following a coronary occlusion is certainly of the greatest importance. In any area of the heart affected by a coronary occlusion, the ultimate fate of the fibers will depend on the degree of anoxemia to which those fibers are subjected. This, in turn, depends on the balance between the blood supply and the

oxygen requirement. If the oxygen requirement can be held down by rest, many fibers which might have become necrotic if forced to contract more frequently and more forcibly may survive. As the blood supply of the heart adjusts itself, these fibers may later have a sufficiently good supply of blood to increase their activity without anoxemia. In borderline cases, whether or not an infarct forms may depend on the load which is put on the heart.

As diagnostic acumen and laboratory methods improve and coronary thrombosis is recognized more often, the pessimistic concept of the prognosis will be modified. When only the more serious and the fatal cases were diagnosed this pessimism was justified. These studies show, however, that the heart is capable of making a better adjustment to thrombosis than has heretofore been expected. The patient can justifiably be encouraged and often can be prevented from acquiring a cardiac neurosis. Many years of enjoyable and even productive existence may follow an episode of coronary thrombosis.

In a heart manifesting severe arteriosclerotic narrowing of the coronary arteries, the muscle fibers may receive an adequate blood supply only when the patient is at rest. An increase in cardiac activity cannot be compensated for by an increase in coronary blood flow. This inadequacy is likely to occur in a heart which has had occlusions of one or of two of the main branches even if only minor or negligible infarcts have formed because of especially well developed anastomoses. Such delicately balanced hearts with a latent coronary insufficiency will be thrown into an acute or chronic coronary insufficiency by any factor which either increases the work of the heart or decreases the coronary blood flow. The work of the heart may be increased by exertion, ventricular tachycardia, infection, hypertensive crises and other factors. Shock, anemia, severe hemorrhage, heart failure and anoxemia from high altitude or from pulmonary conditions decrease the coronary blood flow and the oxygen available to the heart muscle. An electrocardiogram may show no changes when the patient is at rest but will show abnormalities when the muscle fibers become anoxemic. The electrocardiographic changes produced in these hearts by low oxygen tensions [6] and exercise [7] have been used for diagnostic purposes. Repeated spells of acute coronary insufficiency produced by exertion may cause a sufficient degree of anoxemia in some fibers to result in necrosis, and over a long period many focal areas of necrosis may

6. Levy, R. L.; Patterson, J. E.; Clark, T. W., and Bruenn, H. G.: The "Anoxemia Test" as an Index of the Coronary Reserve, J. A. M. A. **117**:2113 (Dec. 20) 1941.

7. Master, A. M.; Friedman, R., and Dack, S.: The Electrocardiogram After Standard Exercise as a Functional Test of the Heart, Am. Heart J. **24**:777 (Dec.) 1942.

develop. This is commonly seen in patients with histories of angina pectoris. A severe degree of coronary insufficiency, even if temporary, may produce an area of infarction such as was found in the heart shown in figure 7.

In hearts with a latent or chronic coronary insufficiency another interesting phenomenon may occur—"infarction at a distance." A heart may have had a thrombosis of the left anterior descending artery and sufficient anastomoses may have formed to prevent the formation of an infarct. The right coronary and the left circumflex branch can take over the area formerly supplied by the anterior descending artery. Months or years later thrombosis may occur in the right coronary artery. The area most affected by this closure may be the area in the left ventricle which was previously supplied by the left anterior descending artery, and it is here that the infarct may form.

SUMMARY AND CONCLUSIONS

This is a presentation of the important observations in a series of 166 hearts in which the coronary arteries were injected and studied post mortem by the Schlesinger method.

The coronary arteries were occluded in 18 hearts. Seven specimens revealed more than one occluded vessel. Thirty-six hearts showed interarterial anastomoses. Anastomoses without occlusion were observed in 21 hearts.

Occlusion with infarction occurred in 13 hearts. Occlusion without infarction was encountered in 5 hearts. Infarction without occlusion of the coronary arteries was found in 2 hearts.

Some hearts showed uniformly hypoplastic arterial systems. In 1 case the hypoplasia was considered a factor in the death of a patient with arteriosclerosis, thrombosis and subsequent myocardial infarction.

In 11 patients over 80 years of age, 9 hearts showed mild to moderate arteriosclerosis and scattered myocardial fibrosis. The other 2 revealed advanced arteriosclerosis, anastomoses, occlusion and infarction.

Anomalies of the coronary arteries involved mainly the left circumflex vessel. In 1 case the right coronary artery was absent.

There is an important relation between the development of anastomoses and the prognosis and treatment of coronary arteriosclerosis and occlusion.

FULMINATING MENINGOCOCCIC SEPTICEMIA ASSOCIATED WITH ADRENAL LESIONS

An Analysis and Discussion of Seven Cases

LIEUTENANT COLONEL J. MURRAY KINSMAN

CAPTAIN C. ANTHONY D'ALONZO

AND

CAPTAIN SIMON RUSSI

MEDICAL CORPS, ARMY OF THE UNITED STATES

FOR HALF a century reports have been appearing in the literature describing a febrile illness which was characterized by the sudden development of a state of shock, by the prominence of hemorrhagic cutaneous rashes, by the remarkably early fatal termination and by the finding of adrenal hemorrhages post mortem. Exceptionally cutaneous eruptions were lacking, and occasionally the adrenal glands were not hemorrhagic.

Voelcker,[1] in 1894, was the first to describe this syndrome, followed by Waterhouse[2] in 1911 and Friderichsen[3] in 1918. In time, the term "Waterhouse-Friderichsen syndrome" came to be applied to any illness of this nature, and this term has now become firmly entrenched in the literature. In none of the cases reported by those authors was the cause of the disease discovered, but in 1916 Maclagan and Cooke[4] reported the occurrence of the syndrome in association with meningococcic meningitis.

There have been reported to date approximately 200 cases of the "Waterhouse-Friderichsen syndrome," with between fifteen and twenty recoveries. Prior to 1939 comparatively few of the reported cases were of proved meningococcic infections. Since then more and more have appeared, especially since 1943. The described pattern of the disease is fairly uniform, but laboratory data have been reported only infrequently and are somewhat conflicting. Postmortem studies in the main have been directed almost exclusively to the adrenal glands.

From the Medical Service, Regional Station Hospital, Fort Bragg, N. C.

1. Voelcker, A. F.: Pathologic Report, abstracted, Middlesex Hosp. Rep., 1894, p. 279.

2. Waterhouse, R.: A Case of Suprarenal Apoplexy, Lancet **1**:577-579, 1911.

3. Friderichsen, D.: Nebennierenapoplexie bei kleinen Kindern, Jahrb. f. Kinderh. **87**:109-125, 1918.

4. Maclagan, P. W., and Cooke, W. E.: Fulminating Type of Cerebrospinal Fever: Pathology and Causes of Death, Lancet **2**:1054-1055, 1916.

It seems worth while to present 7 case histories in an effort to correlate the clinical, laboratory and pathologic factors involved. All 7 patients had fulminating meningococcic septicemia.

CLINICAL DATA

From January 1942 to January 1945, 214 patients with recognized meningococcic infections were admitted to this hospital. Of these, 131 had meningitis and 83 had meningococcemia only. The 7 cases of fulminating infection presented in this report represent 3.3 per cent of the total, an incidence rate which agrees exactly with figures cited in other sources.[5] Two of the cases occurred in January, 2 in March and 1 each in April, August and December. Six of the patients were adult

TABLE 1.—*The Clinical Picture of Fulminating Meningococcic Septicemia*

	Case						
	1	2	3*	4	5	6	7†
Initial symptoms:							
Headache	+	+	..	+	+	+	..
Chill	..	+	..	+	+	+	..
Vomiting	+	..	..	+	+	+	..
"Head cold"	+	+	..	..	..	+	+
Admission temperature, F	103.8	104.6	106.4	..	98.0	99.2	..
Time from onset of illness							
To admission (hr.)	1½	2	..	6½	4½	35	72
To onset of rash (hr.)	3	±15	..	18	<4½	58	24
To onset of shock (hr.)	12	24	..	18	<12	61	..
To onset of coma (hr.)	13½	24	..	..	7	61	..
To death (hr.)	37	26	..	‡	59	‡	72
Distribution of rash (in order of appearance)	Abdomen, chest, back extremities	Entire body	..	"Widespread"	Chest, abdomen, extremities	Chest	..
Stiffness of neck	..	+	..	..	+	..	..
Positive Kernig sign	..	..	..	..	+	+	..
Cyanosis	+	+	..	+	..	+	..

* Patient moribund on arrival—no history obtainable.
† Patient dead on arrival—fragmentary history only.
‡ Patient recovered.

males ranging in age from 19 to 26, and 1 was an 11 month old white male child. One adult was a Negro. Of the 7 patients, 5 died and 2 recovered. The 2 patients who recovered went through just as stormy an illness, up to the point where recovery began, as did the 5 who died. One of the patients, a baby, was dead on arrival at the hospital, and only a meager history was obtainable. Another was dying when admitted, and no history was available. In the other 5 cases, however, reasonably complete histories were obtained. Pertinent data are recorded in table 1.

CLINICAL PICTURE

The illness began from one and a half hours to thirty-five hours prior to admission. Characteristically it was ushered in by headache, chills,

5. Weinberg, L. D., and McGavack, T. H.: The Waterhouse-Friderichsen Syndrome, New England J. Med. **232**:95-101 (Jan. 25) 1945.

vomiting and symptoms of a common cold. The temperature on admission ranged from 98 to 106.4 F. Most of the patients were at first treated as having a simple infection of the respiratory tract. A rash developed in 1 patient within three hours after onset, but as a rule there was none at the time of admission; however, in all of the patients hemorrhagic cutaneous lesions developed later, usually within twenty-four hours after the onset, the rash generally appearing first on the chest and the abdomen. Coincident with the appearance of the rash the temperature rose sharply, and concomitantly or shortly thereafter signs of shock appeared suddenly in the form of extreme weakness, pallor of the face, rapid thready pulse, falling blood pressure and cyanosis of the extremities; the interval of time between the onset of the illness and the change for the worse was usually from twelve to twenty-four hours. A semicomatose state ensued, followed rapidly by coma. Meanwhile the rash spread rapidly—so rapidly that in 1 case the "spots" could actually be seen "popping out" under the eyes of the attendants. From this point on, the patients who died went downhill rapidly, death occurring in from twenty-six hours to three days after the appearance of the first symptoms, while those who recovered gradually began to improve.

The rash will bear further description: Characteristically it consisted of purpuric or petechial lesions, but most of the patients also showed erythematous macules which frequently had petechial or purpuric centers; many of these lesions were tender to pressure. As the rash spread, it tended to become increasingly ecchymotic. One of the recovered patients exhibited a peculiar blotchy blush which appeared and disappeared almost rhythmically. The distribution of the eruption varied markedly; it usually appeared first on the chest and/or on the abdomen, the axillas and the shoulders, later involving the back, the arms and the lower extremities. The face was usually spared in the beginning. As the disease progressed, the lesions extended and coalesced, eventually involving sometimes as much as perhaps 80 per cent of the body surface. Involvement of the conjunctivas and of the oral mucosa was frequently seen, and in 1 case the uvula was black from extensive hemorrhage. In addition to the eruption, patchy areas of cyanosis frequently appeared, and over dependent parts a postmortem type of lividity was often present.

Most writers report that meningeal symptoms and signs are not common and that a lumbar puncture will usually reveal a normal cerebrospinal fluid. The present data do not bear this out. Of the 5 patients on whom a history could be obtained, all had headache as a major presenting symptom; 1 complained of soreness of the neck, and 2 had a positive Kernig sign—the one on admission and the other later in the illness. For 6 of the patients examinations of the spinal fluid were made (table 2), and for 3 of them they were repeated once.

Of the 3 who had only one puncture, 2 had a high cell count; of the other 3, who had two punctures, 2 had a normal cell count from the first specimen of fluid, but all 3 patients had counts showing a manifold increase from the second. It is worthy of note that it was from these same five fluids showing pleocytosis that meningococci were recovered (table 3). The probable reason for the prevailing misconception that the meninges are not involved is that stiffness of the neck

TABLE 2.—*White Cell Counts for Blood and Spinal Fluid*

	Blood				Spinal Fluid			
	White Cells		Neutrophils		White Cells		Neutrophils	
Case	Initial	Later	Initial, per Cent	Later, per Cent	Initial	Later	Initial, per Cent	Later, per Cent
1	7,900	.....	71	..	2	.....	100	..
2	11,950	27,200	86	87	2	2,200	100	97
3	10,750	.....	32	..	500	.....	100	..
4	8,850	33,100	92	97	2	2,240	50	46
5	8,000	26,650	72	84	5,150	.....	98	..
6	18,150	.....	81	..	35	9,000	94	94
7	Patient dead on arrival							

and the Kernig sign are usually absent; hence a spinal puncture is not done or else, when it is, it is done so early in the disease that the fluid is apt to be normal; in either case the possibility of meningitis is then dismissed from mind. To the possible criticism that the first puncture was responsible for the development of the meningitis, attention is called to the fact that in cases 2 and 4 the initial specimens, which each con-

TABLE 3.—*Results of Examinations of Blood and Spinal Fluid for Meningococci* *

	Blood			Spinal Fluid		
Case	Smear	Culture	Group	Smear	Culture	Group
1	+	+	1	0	0	..
2	+	+	1	+	+	1
3	+	+	1	+	+	1
4	0	+	2 A	0	+	2 A
5	0	+	1	+	+	1
6	0	0	..	+	+	1
7	+	+	2 A	0	0	..

* The plus sign indicates that a meningococcus was recovered.

tained two cells, later yielded the meningococcus on culture, showing that even at this stage, before pleocytosis had occurred, the organism had already invaded the meninges.

Rapidly increasing leukocytosis was the rule, the highest count ranging from 18,000 to 33,000.

Blood cultures were positive for meningococci in 6 of the 7 cases (table 3). It is interesting that in 4 cases, all fatal, intracellular diplococci were found on routinely stained blood smears, a finding which

has been referred to in the literature as an "occasional" one. The spinal fluid revealed the meningococcus on either smear or culture or both in 5 of the 7 patients, and in the other 2 the blood culture was positive; hence in every case the cause was established beyond any reasonable doubt.

Of other laboratory findings, those to which attention has been called most frequently are albuminuria, increase in the nitrogenous elements of the blood and changes in the blood electrolytes. In the present cases, studies of the sodium and potassium ions were not made, but in some the nonprotein nitrogen, the creatinine, the chlorides, the sugar and the carbon dioxide–combining power of the blood were determined. The urinary findings are recorded in table 4 and the blood chemistry

TABLE 4.—*Urinary Findings*

	Albumin		Sugar	
Case	On Admission	At Peak of Illness	On Admission	At Peak of Illness
2	+	++	0	0
4	0	+++	++	0
5	++++	++++	Trace	0
6	0	+++	0	+++

TABLE 5.—*Chemical Studies of Blood and Spinal Fluid*

	Blood					
Case	Nonprotein Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Chlorides, Mg. per 100 Cc.	CO_2–Combining Power	Sugar, Mg. per 100 Cc.	Spinal Fluid Sugar, Mg. per 100 Cc.
1	75	1.7	478	..	126	..
			429			
2	86	3.2	396	63	130	75
						52
3	..	...	...	..	...	20
4	39	...	462	43	114	93
	28		531	58		48
			445			
5	75	2.9	479	..	147	54
	92		479			
6	45	0.7	418	49	266	67
	32		413	64		62
7	..	...	...	..	...	..

levels and the sugar content of the spinal fluid in table 5. It is evident that the albuminuria and the azotemia reported by others were present in most instances; however, the 2 recovered patients (4 and 6) showed only slight azotemia although both had severe albuminuria. Glycosuria occurred in 3 patients and hyperglycemia in 4 (unrelated to the intravenous administration of dextrose). No other significant deviation from normal occurred, except the evidence of slight acidosis on the first examination in the 2 recovered patients.

Because the picture of shock is so striking in these patients, table 6 is included, showing the hematologic data pertinent to that condition in 3 cases. None of them showed the hemoconcentration characteristic

TABLE 6.—*Physical Properties of the Blood*

	Blood			Plasma	
Case	Hemoglobin, per Cent	Hematocrit, per Cent	Specific Gravity	Specific Gravity	Total Protein, Gm. per 100 Cc.
4	75	35	1.060	1.025	6.2
	78	36	1.050	1.024	5.8
5	83	38	1.051	1.023	5.5
	85	39	1.052	1.023	
6	91	43	1.056	1.026	6.5
	92	41	1.058	1.030	7.9

of shock. This suggests that the shock exhibited by these patients is not that of blood concentration but is probably of a different nature.

TREATMENT

In 1 instance a sufficiently complete record of the treatment was not available, and in another the patient was dead on arrival. Of the 5 remaining patients 3 died and 2 recovered. These 5 were under treatment long enough to justify a report of the therapy employed,

TABLE 7.—*Summary of Therapy from Beginning of Treatment to Death or to Onset of Recovery*

	Case				
	2	3	4*	5	6*
Treatment period (hours)	10	1	36	50	22
Penicillin (units)	150,000	0	365,000	390,000	290,000
(units per hour)	(15,000)	(0)	(10,000)	(3,800)	(13,200)
Sulfadiazine (Gm.)	11	5	10	12	9
(Gm. per hour)	(1.1)	(5)	(0.3)	(0.14)	(0.4)
Adrenal cortex extract (cc.)	20	40	126	200	2
Desoxycorticosterone (mg.)	0	0	10	15	0
Epinephrine hydrochloride aqueous solution, 1:1,000 (cc.)	0	1	4.5	0.5	1
Epinephrine in oil, 1:500 (cc.)	0	0	4	5	4
Plasma (cc.)	0	0	500	250	500
Insulin (units)	0	0	0	0	70

* Patient recovered.

although 1 was moribund on admission and died two hours later. Table 7 summarizes the treatment of these 5 patients from its institution until death occurred or until recovery began. A detailed account is appended to the paper.

In addition to the specific measures listed, all patients were given isotonic solution of sodium chloride intravenously in quantities which were thought to be sufficient and dextrose (except the patient in case 6).

REPORT OF CASES

CASE 1.—A 21 year old white soldier was admitted to the hospital at 5 p. m. on Aug. 17, 1943. He gave a history of headache, vomiting, coryza and generalized aching beginning about an hour and a half previously. His temperature on admission was 103.8 F. At 8 p. m. it was 105.2 F., by which time the patient was irrational and had a purpuric rash over the abdomen. A diagnosis of meningococcemia was made, and sulfadiazine therapy was begun. At midnight his temperature had reached 106 F. At 5 a. m., August 18, the patient was comatose. Purpuric lesions were then found on the chest, the back and the extremities, and the hands and the feet were cyanotic. The blood pressure was 96 systolic and 64 diastolic and the pulse 160 and respirations 60 per minute. On this day also (August 18) a direct blood smear showed diplococci phagocytosed by neutrophils, and a culture of blood was later reported positive for meningococci group 1. The rash spread; the patient lapsed into a deep coma; pronounced circulatory collapse followed, and the patient died at 4:40 a. m., August 19, approximately thirty-seven hours after onset.

No definite signs of meningitis had been observed. Unfortunately, the spinal fluid was not examined during life, but fluid obtained at autopsy showed slight xanthochromia and contained 2 cells per cubic millimeter; on culture no growth appeared after several days.

The autopsy was performed fifty minutes after death. A macular purpuric rash varying in color from purple to light red was present over the entire body; the borders of some of the macules were indurated. There were also numerous areas of ecchymosis varying from very large to petechial, and hemorrhages were likewise present in the conjunctivas. Beneath the hemorrhagic lesions of the skin there was usually a variable but moderate amount of blood extending into the subcutaneous tissue. Microscopic sections of the skin showed focal collections of blood cells extravasated into the dermis and subcutaneous fat.

A moderate number of small hemorrhages were present in the epicardium, especially around the base of the heart, and beneath the pleura, chiefly around the hilus. Submucous petechial hemorrhages were noted in the ileum and the lower part of the jejunum.

The liver appeared diffusely enlarged (weight, 2,170 Gm.). The capsule was thin, and its surface showed numerous small depressed stellate figures of a red color. The hepatic substance was found to be of a brownish yellow color and of a soft friable consistency. The stellate markings extended for a few millimeters into the substance. Microscopically, focal areas of necrosis and diffuse congestion of the central veins and surrounding sinusoids were evident. There was also a diffuse separation of the hepatic cords from the lining of the sinusoids.

The spleen was large (weight, 440 Gm.) and showed congestion of the pulp on microscopic examination.

Large submucous hemorrhages were found in the renal pelves. In addition, the microscopic examination revealed dilatation of the tubules with hyaline casts in their lumens.

Some hemorrhagic streaks were seen in the periadrenal fat. The adrenal glands were large but of normal contour. Both were heavily infiltrated with blood. The cortex measured 3 to 4 mm. in thickness. Microscopic examination revealed

massive extravasation of blood in the inner layer of the cortex and in the medulla (fig. 1). Hemorrhagic foci were also present in the outer layer (glomerular zone and external half of the fascicular zone). Areas of the cortex not involved by hemorrhage showed definite engorgement of the capillaries. These remnants of cortical tissue were composed of cells with a finely granular or homogeneous eosinophilic cytoplasm. In a few isolated instances, on the periphery of the gland, wherever the architectural details were not totally obscured by extravasated blood, conversion of the solid adrenal cords into "tubular" structures was observed. The lumens of the tubules contained cellular debris, polymorphonuclear leukocytes and,

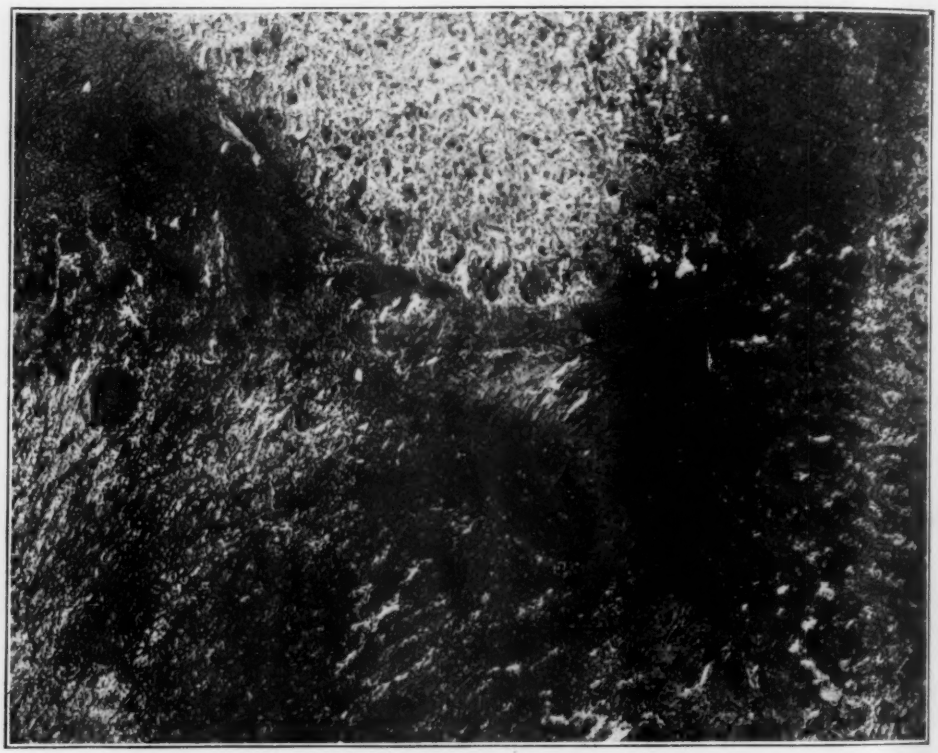

Fig. 1 (case 1).—Section of adrenal gland showing the most intense hemorrhagic changes localized in the reticular zone and the inner portion of the fascicular zones. × 50. (United States Army Medical Museum negative 87500.)

in the zones immediately adjacent to the hemorrhagic areas, red blood cells. The cells lining the lumens had undergone degenerative changes, with fraying of the cytoplasm and pyknosis of the nucleus in evidence. These changes were apparently identical with those of the lesions described by Rich [6] and coexisted with the

6. Rich, A. R.: A Peculiar Type of Adrenal Cortical Damage Associated with Acute Infections and Its Possible Relation to Circulatory Collapse, Bull. Johns Hopkins Hosp. **74**:1-15 (Jan.) 1944.

hemorrhagic changes, although obscured to a great extent by them and by the shrinking away of the cords from the walls of the capillaries. The latter phenomenon resulted in the formation of two parallel lumens, one on each side of a solid cord composed of two rows of cells.

The brain and meninges showed no conspicuous gross lesions. Microscopically, in both there were slight edema and minimal infiltration with cells of inflammatory origin.

CASE 2.—A 29 year old white soldier was admitted to the hospital at 3:30 p. m. on Jan. 22, 1944, about two hours after a sudden onset of weakness, shaking chills, fever, headache, pain in the back and exhaustion. The temperature on admission was 104.6 F. and the leukocyte count 11,950, with 84 per cent neutrophils. Physical examination revealed nuchal rigidity of minimal degree, but Kernig's sign was absent. The pharynx was moderately injected. A roentgenogram revealed that the chest was normal. Meningococci of group 1 were later recovered from the spinal fluid by culture. Early the next morning (Jan. 23) an increasingly widespread, mottled purpuric and ecchymotic rash developed over the entire body, including the face and neck, about 80 per cent of the body surface eventually becoming involved. There were scattered hemorrhagic spots, most of which were large, being an inch (2.5 cm.) or more in diameter. These were present also in the conjunctivas and mouth, the uvula being completely black from hemorrhage. In spite of treatment the eruption continued to spread. The patient became restless and complained of chilliness and burning and soreness "in spots." The lips, the finger nails and the entire skin became cyanotic; the pulse rate was 110, and the blood pressure was 130 systolic and 100 diastolic. Nuchal rigidity had not increased, and Kernig's sign was still absent. The leukocyte count was 27,200 with 87 per cent neutrophils. The temperature was 105 F. At 1:10 p. m. (Jan. 23) the patient became comatose and cyanotic, with rapid respirations. The temperature climbed to 107.8 F. (rectal), and then the respirations dropped to 8 per minute. A direct smear of the blood showed diplococci phagocytosed by neutrophils. The culture of blood was later reported positive for meningoccocci, group 1. In spite of all therapy, however, the patient died at 3:10 p. m., January 23, twenty-six hours after the onset. A second spinal puncture was done at the time of the autopsy, and the fluid contained 2,200 cells.

The autopsy was performed two hours after death. About 80 per cent of the body surface was covered with a macular rash which overlapped the intense postmortem lividity over the dependent parts of the body and which involved completely the upper and lower extremities, the head, the face, the neck and the buttocks. The macules were of a deep purple with some variation in intensity. They appeared to be darker in areas where the skin was thin. The purpuric spots coalesced to a point that only islands of skin an inch (2.5 cm.) or less in diameter appeared normal in color. On the chest and the abdomen were numerous purplish red spots of irregular contour, but fairly large areas of intact skin were still visible. Numerous small, slightly raised and indurated petechiae were scattered over the entire body and were visible through the macular rash. Petechial hemorrhages were present in both conjunctivas. Sections of the skin showed pronounced venous and capillary congestion in the corium and subcutaneous fat. There was slight perivascular infiltration with polymorphonuclear leukocytes and lymphocytes.

Examination of the viscera revealed focal hemorrhages in the pulmonary parenchyma and petechial hemorrhages in the parietal pleura and the parietal and the visceral pericardium. A patch of hemorrhagic infiltration was present under the endocardial lining of the interventricular septum on the left.

The liver weighed 2,700 Gm. There was some spotty variation in color over the capsule, probably of hyperemic rather than of hemorrhagic nature. Microscopic examination showed congestion of the central and interlobular veins. The hepatic cords in the center of the lobules were atrophic. A sprinkling of polymorphonuclear leukocytes was noticed in the sinusoids and in the spaces between the sinusoids and the hepatic cords.

The spleen (weight 230 Gm.) showed congestion of the pulp and a diffuse increase in the number of polymorphonuclear leukocytes.

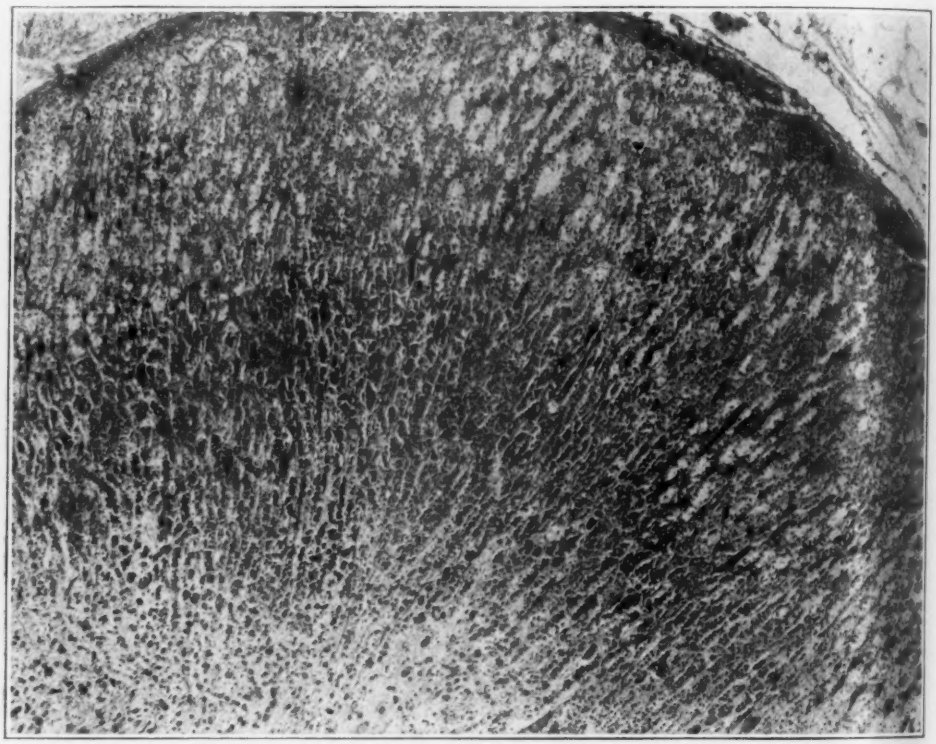

Fig. 2 (case 2).—Section showing "tubular changes" prominent in the external layers of the adrenal cortex. The dark streaks are congested sinusoids. Disruption of the cords and edema of the stroma in the deepest layer are evident. × 50. (United States Army Medical Museum negative 87506.)

The adrenal glands showed no gross hemorrhages. Microscopically (fig. 2), there was pronounced congestion of the sinusoids but no extravasation. The cells in the glomerular zone displayed a vacuolated cytoplasm and appeared of average size, while those in the inner part of the fascicular and reticular zones had shrunk, their cytoplasm being homogeneous and dark and sprinkled with brown pigment. In this case the "tubular" changes in the outer half of the fascicular layer were prominent (fig. 3). The lesion was identical in every respect with that

described and discussed by Rich.[6] The cords in the outer third of the fascicular zone were converted into tubules lined by vacuolated cells, many of which had undergone degeneration with fraying of the cytoplasm and pyknotic changes of the nuclei. Small collections of polymorphonuclear leukocytes were seen in the vicinity of these lesions. In some instances the adrenal cells had disappeared entirely from the inner layer of the cortex (fig. 4), leaving only a recticular stroma between the congested capillaries. The medulla was not remarkable.

The meninges were not conspicuously involved on gross examination, except for questionable cloudiness of the arachnoid along the sulci. Microscopically, there

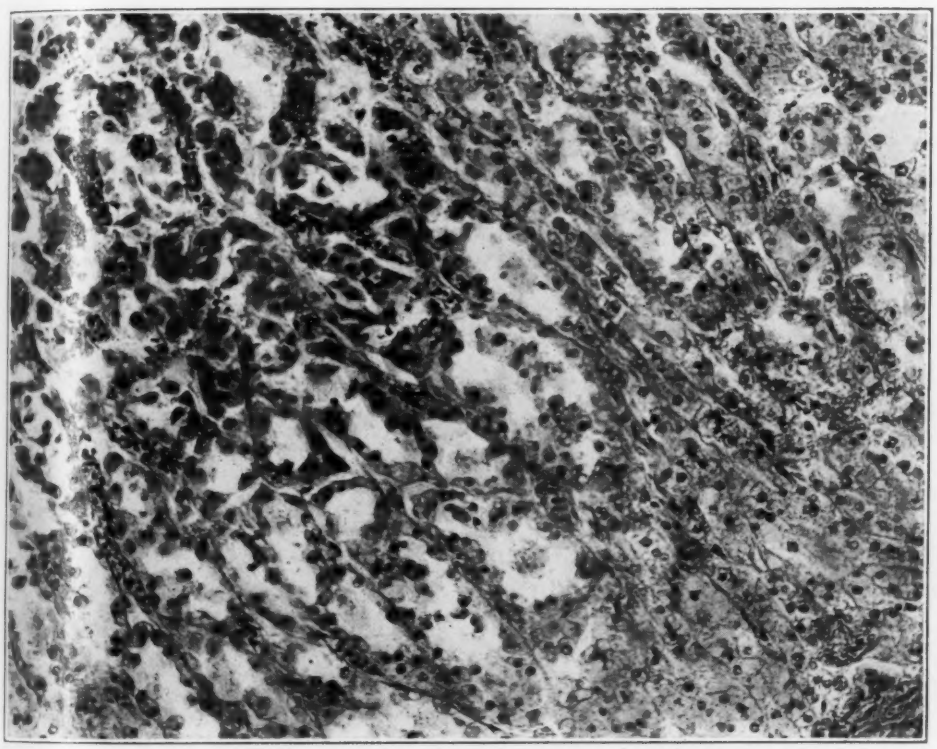

Fig. 3 (case 2).—Section of the superficial part of the adrenal cortex showing detail of the "tubular changes," and congested sinusoids. × 250. (United States Army Medical Museum negative 87502.)

was a fair amount of acute inflammatory cellular exudate in the subarachnoid spaces.

Case 3.—A 19 year old Negro soldier was admitted to the hospital at 11:45 a. m. on March 13, 1944, at the point of death with no available history. His skin was covered with a purpuric rash involving the chest, the face and the back, as well as the lips and the buccal mucosa. Hemorrhagic lesions were also noted

in the conjunctivas. There was no stiffness of the neck. The lungs were normal, and the heart sounds were faint. The temperature (rectal) was 106.4; the blood pressure was unobtainable and the pulse imperceptible. A diagnosis of fulminating meningococcic septicemia was made. The leukocyte count was 10,750, with 32 per cent neutrophils and 68 per cent lymphocytes. Diplococci phagocytosed by neutrophils were seen on direct blood smear, and culture of blood later yielded meningococci, group 1. The spinal fluid contained 500 cells and an abundance of meningococci. The patient died at 2 p. m. on the day of admission, the duration of his illness being unknown.

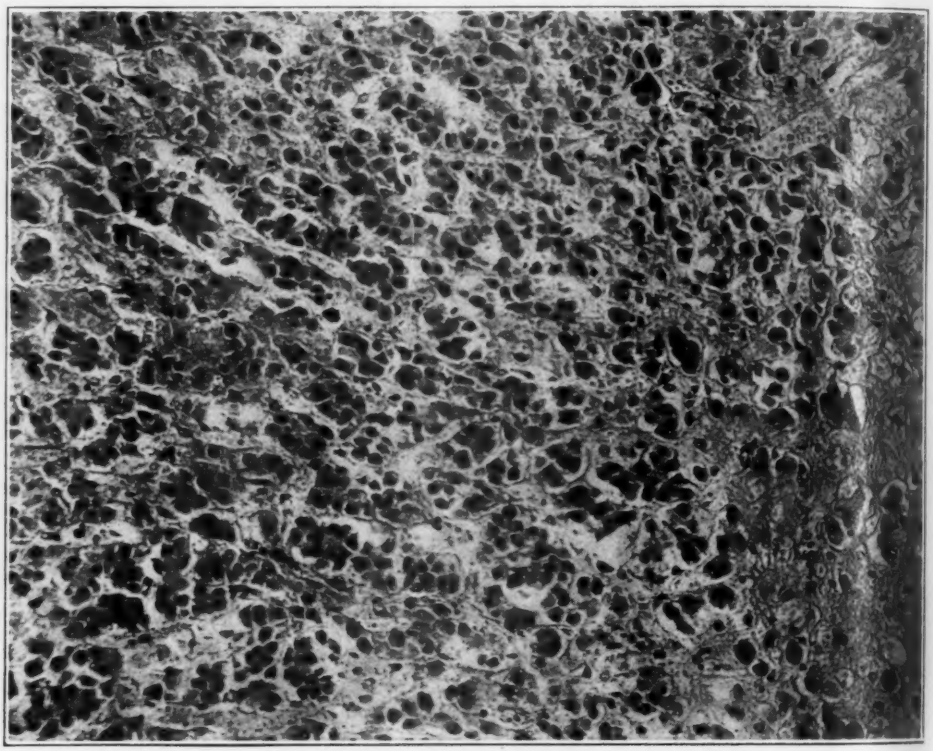

Fig 4 (case 2).—Section of the inner zone of the adrenal cortex showing in detail disruption of the cords, leaving isolated shrunken cells with homogeneous cytoplasm, and edema of the stroma. × 250. (United States Army Medical Museum negative 87501.)

The autopsy was performed two hours after death. The skin was covered with numerous irregular blotchy purplish red spots over the face, the shoulders, the trunk, the abdomen and the extremities but not involving the hands and the feet. Small dark purple petechiae were seen over the forehead and the nasal ridge. Petechial hemorrhages were seen also under the palpebral and bulbar

conjunctivas. Sections through the macular cutaneous lesions revealed congestion of the venules and the capillaries, as well as some edema and cellular infiltration of the corium.

Examination of the viscera revealed petechial hemorrhages under the visceral pericardium of the heart and ascending aorta and under the serosa of the small intestine. There was also some hemorrhage beneath the endocardial lining of the left ventricle over the septum. In the course of the microscopic examination a few small focal hemorrhages were also found in the pulmonary parenchyma and in the thymic interstitia.

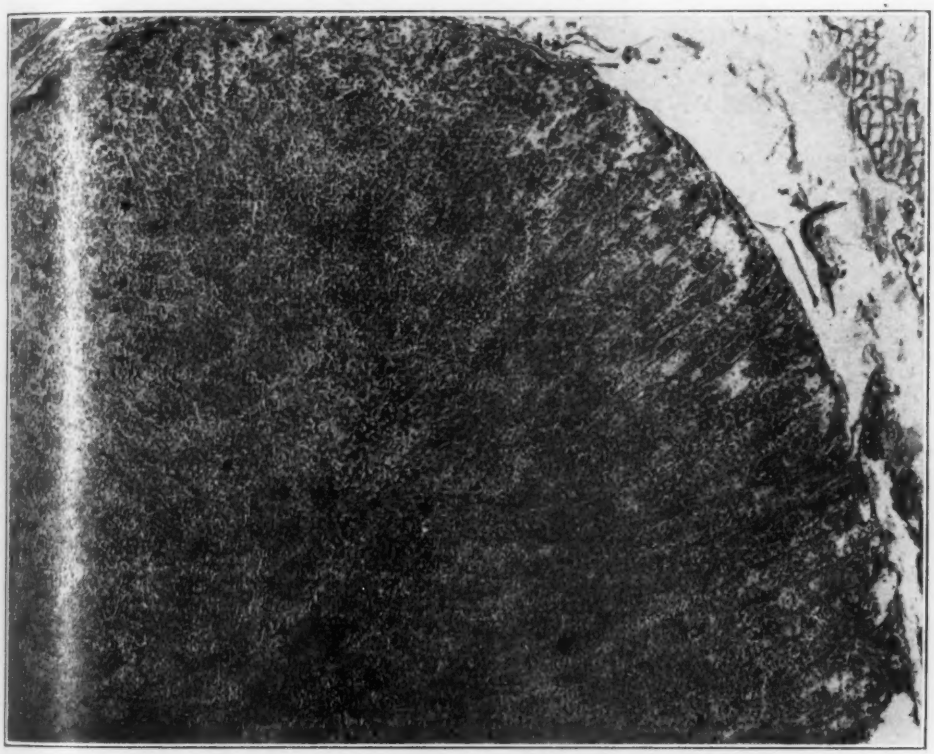

Fig. 5 (case 3).—Section of adrenal gland showing extensive hemorrhage of the inner portion and "tubular changes" in the outer. × 50. (United States Army Medical Museum negative 87499.)

A reddish purple discoloration of both adrenal glands could be seen through the periadrenal fat and capsules. Their cut surfaces presented a diffuse hemorrhagic discoloration of the cortex and the medulla. Microscopic examination revealed diffuse hemorrhagic infiltration, most pronounced in the fascicular and reticular zones of the cortex (fig. 5). In the hemorrhagic zones the normal structure of the adrenal cords and cells was entirely obliterated by extravasated blood (fig. 6). A few islands of adrenal cortical tissue were preserved in the

outer glomerular zone of the cortex (fig. 7), and in these "tubular" changes were slight compared with those in case 1. A few extravasated blood cells were noted in the "tubular" lumens. The adrenal remnants were composed mostly of cells with solid or finely vacuolated cytoplasm. The medulla was not involved in the hemorrhage.

The brain surface showed an intensification of the vascular pattern and a diffuse hemorrhagic discoloration over both temporoparietal regions. Microscopically, a moderate amount of cellular inflammatory exudate was found in the

Fig. 6 (case 3).—Section of inner portion of adrenal gland showing detail of hemorrhagic changes. × 250. (United States Army Medical Museum negative 87496.)

subarachnoid space. A considerable number of red blood cells were mixed with the exudate.

Case 4.—An 18 year old white soldier was readmitted to the hospital at 6:30 p. m. on March 28, 1944, having been hospitalized March 19 to 26 for a common cold. He gave a history of a sudden onset about noon of the day of admission, with headache, shaking chills, nausea, vomiting and pain and tightness in the lower portion of the left side of the chest. The leukocyte count was 8,050, with 67 per

cent neutrophils. Lobar pneumonia was suspected, but a physical examination and a roentgenogram revealed a normal chest. A lumbar puncture was done, the fluid being clear, with two cells; a culture of this fluid later yielded meningococci, group 2A. No therapy was instituted at this time. A later leukocyte count showed 24,300 cells, with 80 per cent neutrophils. On the following morning, March 29, pallor, cyanosis, weakness and a widespread and rapidly increasing purpuric rash rapidly developed; the pulse was imperceptible, and the blood pressure was unobtainable. The leukocyte count was 30,150, with 91 per cent neutrophils. Following therapy, slight improvement occurred, but by midafternoon the blood

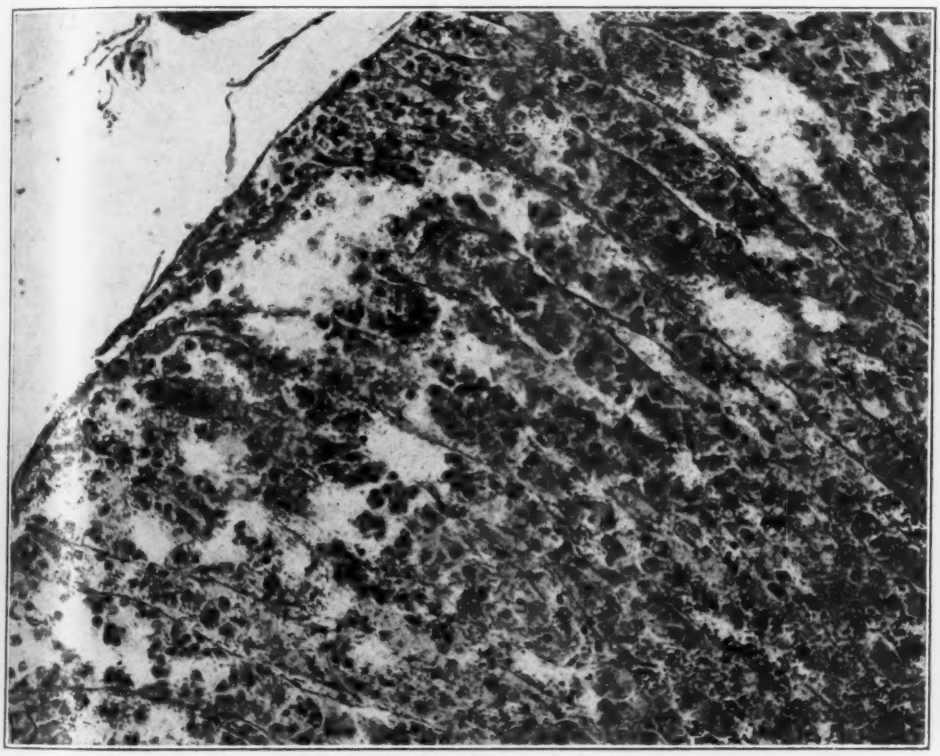

Fig. 7 (case 3).—Section of outer portion of adrenal gland showing detail of the "tubular changes." Red blood cells are seen in the tubular lumens. × 250. (United States Army Medical Museum negative 87504.)

pressure had again fallen to an extremely low figure which could not be recorded, and severe pulmonary edema developed. The patient became moderately stuporous. Oxygen therapy and other measures were followed by some improvement. The condition of the patient remained precarious until 8 p. m. on March 30, when gradual but steady improvement began. He eventually made a complete recovery. Evaluation of adrenal function (sodium chloride restriction, water restriction and dextrose tolerance tests) a month later revealed normal conditions.

CASE 5.—A 26 year old white soldier was admitted to the hospital at 1:30 p. m. on April 13, 1944. He had had one previous admission, on Feb. 5, 1944, with a common cold, from which he made an uneventful recovery, being discharged five days later. Four and one-half hours before his present admission the patient had a severe shaking chill, headache and sore neck. He vomited once. His temperature on admission was 98 F., climbing one hour later to 104 F. The leukocyte count was 12,850, with 88 per cent neutrophils. Numerous petechiae were noted on the chest, abdomen and extremities, varying in size from that of a pinhead to about 3 mm. in diameter, and a few were also seen in the conjunctivas. The Kernig and Oppenheim reflexes were present. The blood pressure was 128 systolic and 72 diastolic.

The clinical course was progressively downhill. The patient became critically ill; marked nuchal rigidity developed and he became semicomatose about 4 p. m. The temperature rose to 105 F. A spinal puncture revealed cloudy fluid containing 5,150 cells per cubic millimeter, with 98 per cent neutrophils, and smears and culture were positive for meningococci, group 1. The same organisms were recovered from the blood and the nasopharynx. Sulfadiazine therapy was begun at 6 p. m., April 13. By 8:30 a. m. on April 14 the blood pressure and the pulse were imperceptible. At 6:30 p. m. the leukocyte count was 26,650, with 84 per cent neutrophils, and the blood pressure was 80 systolic and 60 diastolic. At 8:30 a. m. on April 15 the patient suddenly became much worse; the rash increased, and large purpuric lesions developed. The nonprotein nitrogen of the blood had increased from 75 mg. per hundred cubic centimeters on the fourteenth to 92 mg. on the fifteenth; the creatinine of the blood was 2.9 mg. per hundred cubic centimeters, and the blood sugar was 148 mg. per hundred cubic centimeters. Urinalysis showed albumin (4 plus) with 25 to 30 red blood cells per high power field, a few white blood cells and granular casts. In spite of all therapy the patient died at 8 p. m. on April 15, fifty-nine hours after onset.

The autopsy was performed thirteen hours after death. The cutaneous rash in this case showed a complete predominance of the petechial component over the purpuric. Numerous petechiae averaging 2 mm. in diameter were scattered over the chest, the abdomen, the arms, the thighs and the back. Only a few purpuric spots were seen; these were limited to the legs and the forearms and averaged about 2 cm. in diameter. Sections of the skin revealed edema of the corium and a slight diffuse lymphocytic infiltration with focal perivascular condensation. The sebaceous glands had undergone partial necrosis and were diffusely infiltrated with leukocytes. A few dilated arterioles below the corium were plugged with compact collections of fibrin, red blood cells and leukocytes; these were thought to be thrombi, responsible for the petechial lesions in the skin.

The pleural cavities each contained 300 cc. of clear fluid. The lungs were exceedingly wet, heavy and congested. There were patchy areas of increased consistency, presenting a mottled gray color on the cut surface, especially numerous in the posterior parts of the lungs. The sections showed edema, with fluid and fibrinopurulent exudate in the alveolar and bronchiolar lumens. The distribution of the exudate was patchy and its density variable.

The heart weighed 420 Gm. The myocardium was of a flabby consistency and a grayish tan; its cut surface revealed yellow and reddish purple mottling, and in some instances coalescent rounded yellow areas of discoloration were scattered throughout its superficial third, while the purplish red discoloration was most conspicuous midway between the pericardium and the endocardium. The papillary muscles in the left ventricle were involved in the changes, hemorrhagic spots being

present. Microscopic examination of the heart confirmed the gross evidence of acute myocarditis, revealing degeneration of the muscle fibers and polymorphonuclear and mononuclear leukocytes infiltrating the interstices. The degenerative changes in the fibers were far more pronounced than the cellular infiltration of the interstices.

The gastrointestinal tract was not remarkable except for esophageal erosions.

The liver weighed 2,180 Gm. The central veins and sinusoids were congested. The cell borders were indistinct, and the portal spaces were in some instances being infiltrated by leukocytes.

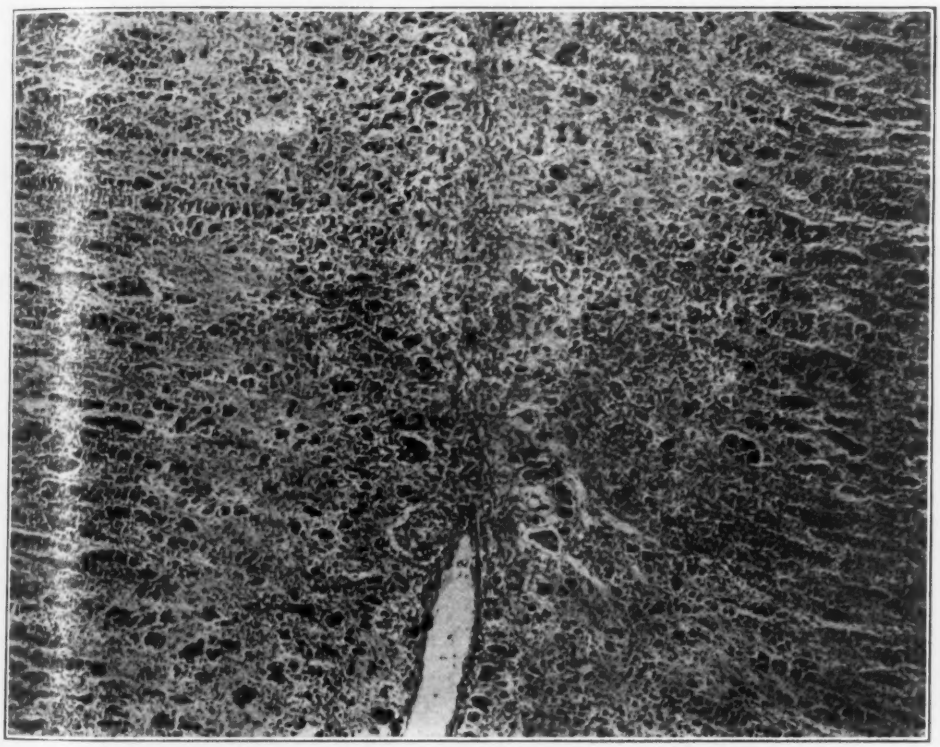

Fig. 8 (case 5).—Section of adrenal gland showing extensive degeneration of cells in inner zone of cortex. × 50. (United States Army Medical Museum negative 87505.)

The spleen (weight 320 Gm.) showed many infarcts. On microscopic examination thrombi were seen in many arteriolar lumens.

The kidneys weighed 200 Gm. each. The capsule stripped with some difficulty, tearing off particles of tissue. On the cut surface the cortex was pale tan; the structural details were somewhat blurred, but the demarcation between the cortex and the pyramids was distinct. The histologic sections showed ischemic glomeruli and distention of Bowman's capsules and the tubules with fuzzy eosinophilic debris.

Some of the tubules contained compact hyaline casts, and the tubular epithelium was flattened. The capillaries in the pyramids were congested.

The adrenal glands showed no gross hemorrhages. A brown zone was noted between the gray medulla and the bright yellow cortex. Microscopic examination revealed a zone of degeneration involving the reticular and inner fascicular layers (fig. 8). There were marked disruption and fragmentation of the cords. The individual cells were shrunken, with frayed cell outlines, and the cytoplasm was scanty and impregnated with fine and coarse brown pigment. In many places only a small amount of cellular debris and a delicate reticular stroma were seen. The

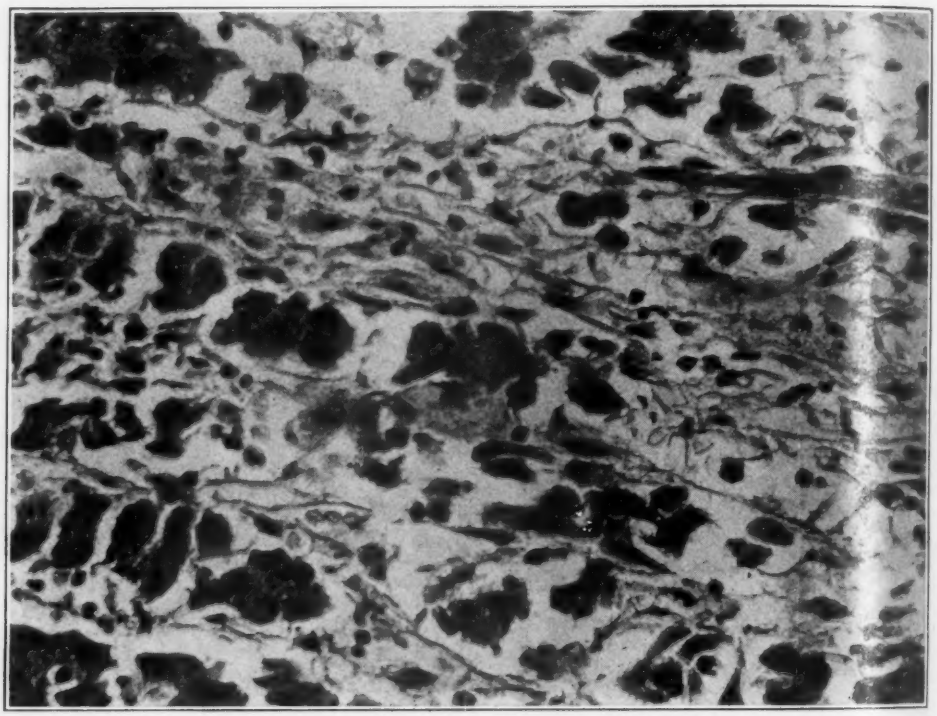

Fig. 9 (case 5).—Section of inner zone of adrenal cortex showing in greater detail the degeneration of the cells. × 500. (United States Army Medical Museum negative 87620.)

cells in the external layers of the cortex were shrunken and presented a solid homogeneous cytoplasm. There was also evidence of "tubular" degeneration although much less conspicuous than in the previous case. The "tubular" changes of the outer fascicular layer were overshadowed by the disruption of the cords and the degeneration of the cells in the inner layers (fig. 9). The sinusoids, especially in the degenerated zone, were greatly distended and filled with blood, with a few escaped red blood cells visible outside their walls. The border zone between the degenerated and the external layers was infiltrated by lymphocytes

and occasional polymorphonuclear leukocytes. The medulla showed shrinkage of the individual cells, as well as foci of lymphocytic infiltration.

The leptomeninges were cloudy over both hemispheres of the brain and on microscopic examination revealed the typical changes of acute meningitis. The pituitary gland showed hyperemia of the anterior lobe.

CASE 6.—A 19 year old white soldier was admitted to the hospital at 10 a. m. on Dec. 3, 1944. On admission, he stated that he had had a "cold" for the preceding week, but thirty-five hours prior to admission he experienced some shaking chills and vomited. His temperature on admission was 99.2 F.; the pulse rate was 90, and the respirations were 18 per minute. Physical examination revealed essentially normal conditions except some slight injection of the pharynx. On December 4 at 9 a. m. there was a recurrence of the shaking chills and vomiting, which became increasingly severe. These were accompanied with malaise, vertigo and a generalized throbbing headache. His temperature (rectal) then was 103 F.; the pulse rate was 100, and the respirations were 20 per minute. At this time the chest exhibited scattered macular rose spots of varying sizes, which were not painful and did not blanch on pressure. Slight injection of the pharynx was still noted. Other physical findings, including the neurologic ones, were normal. The blood pressure was 130 systolic and 80 diastolic. A leukocyte count was 18,150, with 81 per cent neutrophils, and a blood culture failed to show growth of any organism. A spinal puncture yielded clear fluid with normal dynamics and containing 35 cells per cubic millimeter, of which 94 per cent were neutrophils. A culture later yielded meningococci, group 1. A diagnosis of meningococcemia was made, and treatment with penicillin was begun. At noon on December 4, three hours later, the patient suddenly grew pale, weak, listless, sluggish and lethargic, and the blood pressure dropped to 120 systolic and 50 diastolic. The macules increased in size and number, many developing petechial centers, and other petechial lesions appeared. Huge macular blotches began to appear and disappear periodically over the entire body but mainly over the chest, the arms and the neck. Cyanosis was present. The Kernig and great toe reflexes became positive. Stupor and coma ensued. Retention of urine developed, followed by incontinence. A catheterized specimen showed sugar (3 plus) but no acetone or diacetic acid. Chemical analysis of the blood revealed nonprotein nitrogen 45 mg. and sugar 266 mg. per hundred cubic centimeters, but the chlorides, the carbon dioxide–combining power and the creatinine were within normal limits. Nuchal rigidity became noticeable. The temperature climbed to 104 F.; the pulse became feeble and imperceptible; the respirations rose to 28, and the blood pressure dropped to 100 systolic and 40 diastolic. Spinal puncture at this time showed a cloudy fluid, under moderately increased pressure, with 9,000 cells per cubic millimeter, of which 94 per cent were neutrophils. Insulin was added to the routine therapy. The patient's condition remained precarious until 9 a. m., December 5, when definite improvement was noted. On the morning of December 7 the patient was rational, and improvement was apparent. Convalescence from this point on was steady, and recovery was complete.

CASE 7.—An 11 month old boy was dead on arrival at the hospital on Dec. 19, 1944. A fragmentary history was obtained from his parents of a mild acute infection of the respiratory tract beginning three days before admission. A rash, described by his mother as "little red bumps under the skin," appeared on December 17, but the general condition of the child did not appear alarming to the parents until December 18, when a high fever developed. The rash assumed a dark color

and began spreading rapidly. The child apparently died on his way to the hospital, three days after the onset.

Meningococci group 2 A were later recovered from blood taken for culture at autopsy.

The autopsy was performed fifteen hours after death. The patient was well developed and well nourished. The skin was covered with a macular purpuric rash consisting of irregularly shaped, deep purple blotches scattered over the entire body but more pronounced over the face, the shoulders and the extremities

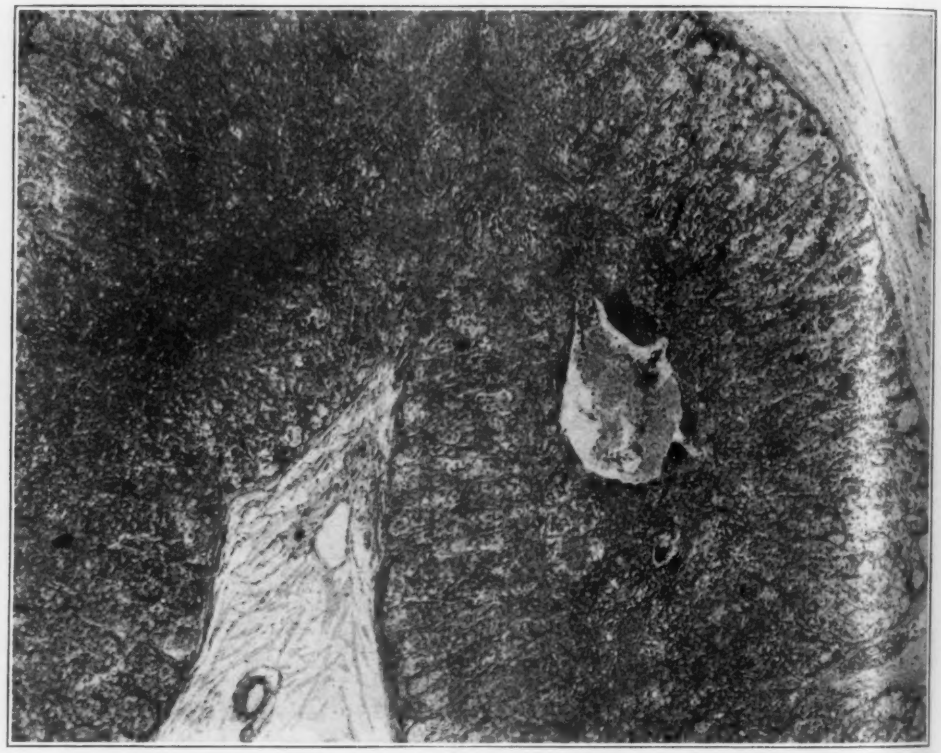

Fig. 10 (case 7).—Section of adrenal gland showing hemorrhage in inner zone and "tubular changes" in outer zone. × 50. (United States Army Medical Museum negative 87498.)

while relatively inconspicuous over the chest, the abdomen and the back. The central portion of some of the macules was a pale yellowish gray, while the outer portion consisted of a distinct dark hemorrhagic zone, which faded gradually into the surrounding skin. The hemorrhagic discoloration extended into the corium. Sections of the skin revealed arteriolar thrombi in the corium and in the superficial layer of the subcutaneous fat, with patches of a diffuse infiltration of polymorphonuclear leukocytes in the corium and epidermis above the thrombosed

vessels. Bacterial stains revealed the presence of gram-negative intracellular diplococci.

The viscera apart from the adrenal glands were not remarkable except for slight congestion and patchy edema of the lungs and some congestion of the hepatic sinusoids. There was also a diffuse sprinkling of polymorphonuclear leukocytes throughout the hepatic tissue.

Both adrenal glands showed diffuse hemorrhagic discoloration of the parenchyma. Microscopic examination revealed diffuse hemorrhages involving especially the inner cortical layers (fig. 10). The sinusoids were congested, and the cortical

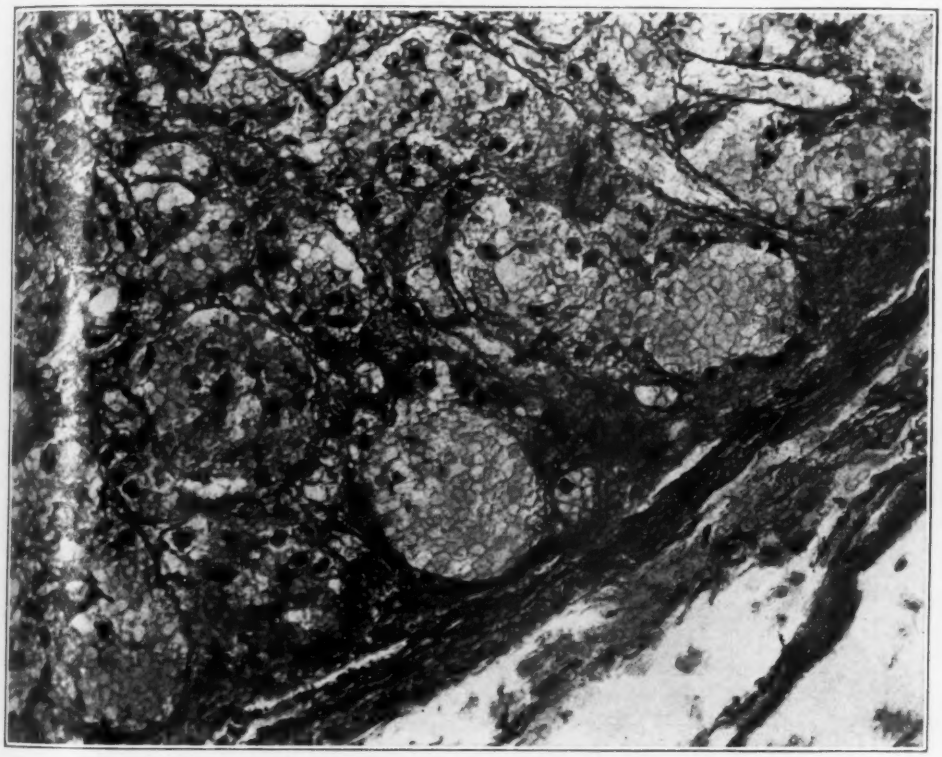

Fig. 11 (case 7).—Section of external layer of adrenal cortex showing detail of "tubular changes." The lumens are packed with escaped red blood cells. Some of the epithelial cells appear flattened, and others are missing. × 450. (United States Army Medical Museum negative 87495.)

tissue was composed of cells with solid or finely vacuolated cytoplasm. Here also "tubular" changes were observed in a few instances in which small islands of cortex escaped flooding with blood. At some points, even in the hemorrhagic areas of the glomerular zone, the glomerular structures assumed a circular arrangement resembling a cross section of a tubule, with flattened adrenal cells forming the lining, the lumen being tightly packed with red blood cells (fig. 11). In some

isolated instances the lining cells were missing entirely, while in others they displayed degenerative changes.

The meninges did not reveal any conspicuous lesions grossly, but microscopically there was a moderate amount of inflammatory cellular infiltration in which polymorphonuclear leukocytes, large monocytes and a few lymphocytes participated.

NOTE.—All the cranial, thoracic, abdominal and pelvic viscera were examined grossly in each autopsy. Histologic sections of the following organs were prepared and examined: skin, heart, aorta, lungs, liver, pancreas, spleen, lymph nodes, thymus and adrenal and pituitary glands. Sections of the trachea, the gastrointestinal tract, the gallbladder, the prostate, the bladder, muscle, bone marrow and the thyroid gland were prepared only if the gross appearance of the tissues suggested a deviation from normal. Sections of the pituitary gland were missed in case 2, of the thymus and lymph nodes in case 5 and of the aorta and spleen in case 7. For the sake of brevity only the deviations from gross and microscopic normal appearance are reported in the preceding pages.

COMMENT

For many years various diseases have been reported under the term "Waterhouse-Friderichsen syndrome." These have included not only meningococcic but also other infections, acute purpuras and not infrequently diseases in which the cause was undetermined, though latterly the expression has tended to become synonymous with fulminating meningococcic infections. In many instances postmortem examinations either were not made or else failed to reveal adrenal hemorrhage, and in a few cases the patient survived, yet the illness was still so labeled. Obviously the term is erroneously applied under such circumstances, for the one common denominator in the cases reported by both Waterhouse and Friderichsen was massive adrenal hemorrhage. Since it is inconceivable that a patient can long survive after his adrenal glands have been destroyed, it follows that the diagnosis is essentially a pathologic one and that it should be reserved exclusively for those patients in whom adrenal hemorrhage is demonstrated—if, indeed, it is to be used at all. Certain recent publications [7] indicate that there is already developing a tendency to regard this matter in a similar light.

If one wishes to continue to use the term "Waterhouse-Friderichsen syndrome," then cases 1, 3 and 7 certainly fall within that category, inasmuch as the one cardinal and pathognomonic criterion of that condition, extensive adrenal hemorrhage, was present; also, they exhibited another, near cardinal sign, hemorrhagic cutaneous phenomena. By the same criterion, cases 2 and 5 cannot be properly included, inasmuch as massive adrenal hemorrhage was not present, nor cases 4 and 6, because the patients survived and hence the condition of their adrenal

7. (*a*) Pratt-Thomas, H. R.; Kelley, W. H., and Gazes, P. C.: Fulminating Meningococcemia (the Waterhouse-Friderichsen Syndrome), South. M. J. **38**: 229-235 (April) 1945. (*b*) Adams, F. D.: Some Clinical Aspects of Meningococcic Infection, Ann. Int. Med. **20**:33-44 (Jan.) 1944.

glands was not known. But all 7 of these patients did have two things in common: a proved meningococcic infection and a fulminating clinical course. Hence they are all properly labeled as instances of "fulminating meningococcic septicemia." [8]

In the 2 patients in whom autopsy revealed the absence of massive adrenal hemorrhage, there were, nevertheless, adrenal changes consisting of zonal degeneration and severe congestion; moreover these were located in the same layers where in the other 3 cases the intensity of the hemorrhagic changes was most striking. Pathologically, therefore, there were essentially two types of adrenal changes: degenerative and hemorrhagic. The degenerative changes consisted in disruption of the cortical cords, death and lysis of individual cells and congestion and edema of the stroma, involving the entire reticular and the inner half of the fascicular zones (figs. 2, 4, 8 and 9). The outer fascicular and glomerular layers presented channeling of the adrenal cortex cords resulting in the formation of "tubules" (figs. 2 and 3). The hemorrhagic phenomena were most intense in the same areas where the degenerative changes were most pronounced in the first group (fig. 1), but they extended also into the medulla and into the external layers of the cortex where leaking of blood into "tubular" lumens (fig. 7) or packing of the lumens with extravasated blood (fig. 11) was evident. The clinical course of patients presentnig the degenerative lesions was not essentially different from that of patients showing the hemorrhagic. It seems logical to believe that these two types of changes are stages in the same process, the first representing an early, probably still reversible phase and the latter the terminal, irreversible phase.

The cause of the circulatory collapse, which is such an outstanding phenomenon in this disease, has been the subject of much speculation. It seems unreasonable to place the entire blame on the exhaustion of hormonal supply associated with the adrenal lesions, even though the latter are usually of a high degree, as they were in the fatal cases reported here. In certain instances, injuries of other organs may be responsible to a greater or less degree: In case 5, for example, there was severe injury of the myocardium, and other conditions observed in this case (pulmonary edema and bilateral hydrothorax) were consistent with circulatory failure of cardiac origin. Meningeal inflammatory changes can scarcely be held responsible for the collapse, for although they were invariably present in all the cases yet they did not appear to be so extensive and so intense as in other fatal cases of frank meningococcic meningitis seen by us. The other pathologic developments, such as focal hepatitis, splenic infarcts and the congestive phenomena of various

8. The term "meningococcic septicemia" is used rather than "meningococcemia" to lend emphasis, by the use of the word "septicemia," to the existence of sepsis, or poisoning.

organs, were no more pronounced than they usually are in acute septicemias in general. It seems probable that in these fulminating infections no one organ or system of the body can be said to be injured so severely as to be by itself entirely responsible for the circulatory failure. This is not to say, however, that the deprivation of the body of the normal adrenal hormonal supply may not play some part in its genesis. In discussing the role of the "tubular changes" in the adrenal glands, Rich [6] stated that these lesions may "be at least a contributing factor in some of the instances of circulatory collapse that occur during severe acute infections." This point of view seems reasonable, and it is probable that the cause of the collapse is primarily a widespread injury of many tissues as a result of the toxic action of the bacterial products; the adrenal glands share in this injury, and the physiologic disturbances ensuing therefrom play a part, but only a part, in the resulting catastrophe. This point of view is supported by the work of Ebert and Stead,[9] who, after studying the nature of the shock accompanying acute infections, came to the conclusion that it does not have the same mechanism as hemorrhagic or traumatic shock because the volume of plasma is not decreased and transfusions are not beneficial; nor is it due to a diminished venous return to the heart from pooling in the small vessels, because filling the venous system does not improve the circulation.

There is another factor which theoretically may play a role in the circulatory collapse, either directly by its influence on metabolism in general or indirectly through the part it plays in adrenal metabolism—vitamin C. It is known that this vitamin is particularly abundant in the adrenal glands and that in acute infections its concentration in the body rapidly diminishes.[10] It has been observed that its oral or parenteral administration in cases of Addison's disease may strikingly diminish the pigmentation and that in 3 patients with Addison's disease there was a definite parallelism between the degree of vitamin C deficiency and the severity of the disease.[10] Although no data bearing on its metabolism in fulminating meningococcemia have been encountered, the possibility that it may be involved in the collapse is worth mentioning, and it is suggested that it would be worth while in the future to administer large doses of ascorbic acid to patients with this disease.

In attempting to interpret the pathologic physiology of the adrenal glands in this illness several factors may be considered. Normally, the adrenal cortical cells, especially in the outer layers, are filled with

9. Ebert, R. V., and Stead, E. A., Jr.: Circulatory Failure in Acute Infections, J. Clin. Investigation **20**:671-679 (Nov.) 1941.

10. Bicknell, F., and Prescott, F.: The Vitamins in Medicine, London, William Heineman, Ltd., 1942, chap. 6, p. 300.

lipoid globules, which when viewed microscopically after fixation and dehydration appear as vacuoles. It is generally believed that this lipoid either contains the hormone or is the substance from which it is derived and that this globular state represents a storage phenomenon.[11] Now, experimental work and pathologic observation have demonstrated that not only in animals subjected experimentally to various metabolic disturbances [12] but also in persons with overwhelming infection and cachexia [13] there is a pronounced diminution of the lipoid content of the adrenal cortex. The lipoid material is supposedly released into the circulation,[11] and the cells then degenerate, their cytoplasm changing from its normal globular to a more homogeneous or granular state.[14] These changes were obvious in cases 3 (fig. 7) and 5 (fig. 8), and in the others they were suggested in the preserved islets of cortical cells between the hemorrhagic areas, although largely obscured by the hemorrhage itself (fig. 11).

The cortical cell originates in the outer layer of the cortex, and as it ages it travels centripetally, eventually undergoing degeneration, death and lysis in the innermost layer. This process is a slow and orderly one, and regeneration of new cells preserves the integrity of the tissue. The degeneration of the cell in the reticular layer is, then, a normal phase—the final one—of the cell's life cycle. It has been demonstrated that an acute infection increases the demand on the adrenal cortex, thus bringing about the cytoplasmic changes described.[11] If the infection becomes overwhelming, as in fulminating meningococcemia, the demand is still further increased, so that the natural aging process of the cell is accelerated beyond the natural regenerative capacity of the tissue to replace it. As a consequence the cell dies before reaching its normal site of lysis. Its death in the outer layer permits serum to escape through the vacancy which it leaves; hence channeling or "tubule" formation results, while the death of many (older) cells in the deeper layers results in the creation of a wide zone of degeneration involving the inner half of the cortex. This zone now becomes a locus minoris resistantiae due to extensive loss of support to the walls of the sinusoids. This factor, combined with a systemic increase in capillary permeability resulting from the infection, may explain the occurrence of hemor-

11. Zwemer, R. L.: A Study of Adrenal Cortex Morphology, Am. J. Path. **12**:107-114 (Jan.) 1936.

12. Sarason, E. L.: Morphologic Changes in the Rat's Adrenal Cortex Under Various Experimental Conditions, Arch. Path. **35**:373-390 (March) 1943.

13. Sarason, E. L.: Adrenal Cortex in Systemic Disease, Arch. Int. Med. **71**: 702-712 (May) 1943.

14. Maximow, A., and Bloom, W.: A Text Book of Histology, Philadelphia, W. B. Saunders Company, 1930.

rhages in some cases of fulminating meningococcemia. Also, the loss of individual cells in the outer layers of the cortex permits blood cells to be extravasated into the "channel." The process may be aided by the postural factor in a patient with failing circulation, lying prone on his back, as the blood pools in the dependent parts of the body, which would include the adrenal glands. Of course, it is possible that the actual hemorrhage may be simply a terminal condition, having little or no causal relationship to the production of death.

This concept, then, of the course of events in these patients is that the picture is, from beginning to end, one of overwhelming septicemia with acute vasomotor collapse. Among others, adrenal changes occur, consisting at first in degenerative phenomena manifested by "tubular" degeneration in the outer cortical layers with more pronounced lesions in the inner zones. Lysis of many of the individual cells follows, resulting in disruption of the cords. Engorgement and edema follow to replace the vacuum and to dispose of the debris left from the degenerative process. It is assumed that at this stage the adrenal changes are reversible and the patient may recover (the recoveries of the patients in cases 4 and 6 probably exemplify this), or the infection may be so overwhelming that the patient may die nevertheless before adrenal hemorrhage has had a chance to occur (as in cases 2 and 5), or adrenal hemorrhage may result, following which recovery is impossible (cases 1, 3 and 7). This interpretation would explain the variation in the pathologic observations of the reported cases as well as the recoveries from fulminating meningococcic septicemia.

So far as the pathogenesis of the rash is concerned, the purpuric component is probably due to loss of tonus with consequent congestion in the corium, which, in conjunction with increased capillary permeability, results in rupture and hemorrhage; the petechial component is probably due to the presence of thrombi in the arterioles beneath the corium (as noted in cases 5 and 7); the periodically appearing and disappearing macular blotches (noted in case 6), to fluctuations in vasomotor tone, and the cyanosis of dependent parts, simply to peripheral vasomotor collapse with venostasis.

It has been observed that meningococcic infections are not infrequently accompanied with transient glycosuria and/or acetonuria.[15] In a review of 125 cases at this hospital it was found that in 12 the patients showed transient glycosuria. Of the 7 patients with fulminating infection here reported on, 2 had significant amounts of sugar in the urine while 4 had at least one blood sugar level higher than 120 mg. per

15. Ferguson, F., and Barr, D.: Glycosuria in Meningitis, Ann. Int. Med. **21**: 173-186 (Aug.) 1924.

hundred cubic centimeters. The elevation was not marked in 2 of these, but in 1 (a survivor, case 6) it was 266 mg. per hundred cubic centimeters. The pancreas and the pituitary gland were studied in all but 1 of the cases brought to autopsy, with the problem of this hyperglycemia in mind, but they showed no significant changes in any instance; however, the hypothalamic areas were not studied at all. In 1 patient (case 5) with a blood sugar content of 147 mg. per hundred cubic centimeters the liver did show some changes, with congestion of the central sinusoids and some areas of infiltration of the portal spaces; however, it is doubtful that the changes were intense enough to be responsible for any significant disturbances of the carbohydrate metabolism. This study can furnish only conclusions of a negative nature concerning the cause of the disturbance.

It is important to emphasize the fact that when first seen these patients often appear to be suffering from nothing more than an ordinary infection of the respiratory tract. Insufficient stress has been laid on this point by most writers. An exception is Adams,[7b] who does call attention to it and who has written a vivid description of the characteristic clinical picture in this disease. Of the 7 patients reported on here, 4 were initially admitted to respiratory disease wards. In this hospital every new officer, on being assigned to such a ward, is cautioned to be on the alert for these cases. Freqeunt inspection of the entire body for eruptions is an essential for early diagnosis.

The principles of treatment in fulminating meningococcemia are:

(*a*) To combat the infection, with sulfadiazine or penicillin or both.

(*b*) To combat shock, with adrenal cortex extract, epinephrine, plasma and sodium chloride.

(*c*) To combat anoxemia, with oxygen.

(*d*) To combat special complications as they arise (as hyperglycemia, with insulin).

An analysis of the data in this report (table 7) fails to uncover any one factor to which recovery may be attributable. For instance, the largest dose of penicillin per hour was given in a fatal case; likewise, while one recovered patient received 116 cc. of adrenal cortex extract during the period of acute illness, the other received only 2 cc., and a patient in 1 of the fatal cases was given 40 cc. The only fact which is suggestive in the present data is that both the recoverd patients were given 500 cc. of plasma, while in the fatal cases one patient received none and the other only 250 cc. In view of the lack of any evidence of hemoconcentration in the 3 patients on whom studies were made and of the experimental evidence that in cases of acute infections the volume of plasma is not decreased,[9] it seems probable

that the recovery of the 2 patients who had plasma was coincidental and not due to the plasma. The question as to whether adrenal substitution therapy is of value cannot be answered by this study. The theory has been advanced that antitoxic serum might have a definite place in therapy,[16] but it was not used in any patient in this series. The idea that ascorbic acid may be beneficial has been presented earlier in this paper. A proper evaluation of therapy would ideally depend on a plan of treating a number of patients identically except for a variation of only one factor at a time in different groups. However, the infrequency of the disease and the fact that only an occasional patient recovers make such a plan totally out of the question. The ultimate evaluation of the best treatment for this disease will probably have to rest on a statistical analysis of the therapy in the reported survivals in comparison with that in the fatal cases. Meantime, it would seem that the main effort of therapy should be directed, early and vigorously, toward overcoming the infection and the toxemia, with supportive measures occupying a secondary though not unimportant place, in the hope that the patient will thereby be given a chance to recover before irreversible changes, such as hemorrhages, occur in the adrenal glands.

SUMMARY AND CONCLUSIONS

The confusion surrounding the use of the term "Waterhouse-Friderichsen syndrome" is pointed out, and it is suggested that it either be abandoned entirely or else be rigidly restricted to those patients presenting the clinical picture of an acute fulminating febrile disease and in whom adrenal hemorrhages are found post mortem. Acute septicemias of proved cause should be called "fulminating septicemia."

Seven cases of proved fulminating meningococcic septicemia are reported, in which 2 patients recovered. The clinical and pathologic observations are presented in detail.

In the beginning the illness was usually diagnosed as an ordinary infection of the respiratory tract. An eruption developed within three to twenty-four hours after the onset, the rash appearing in the form of erythematous macules, petechiae, purpura or a simple erythematous blush, usually in combination. Signs of shock appeared in twelve to twenty-four hours. Symptoms suggesting meningitis were usually present: Five of the 7 patients had an increased number of cells in the spinal fluid, pleocytosis developing under observation in 3 patients; cultures of the spinal fluid of the same 5 patients yielded the menin-

16. Boger, W. P.: Fulminating Meningococcemia: Demonstration of Intracellular and Extracellular Meningococci in Direct Smears of Blood, New England J. Med. **231**:377-404 (Sept. 14) 1944.

gococci. Cultures of the blood of 5 patients were positive for meningococci. Albuminuria and azotemia were the rule, and hyperglycemia was present in 4 of the 5 patients on whom a dextrose tolerance test was made; none of the patients showed significant acidosis. In no instance was hemoconcentration discovered.

In 3 of the fatal cases adrenal hemorrhage was shown, while in the other 2 adrenal changes were present, consisting of zonal degeneration and conspicuous congestion in the inner layers of the cortex, with "tubular changes" in the outer layer. In 1 case there were myocardial changes which were sufficient to have caused a circulatory collapse, but in the others there were no significant changes apart from those in the adrenal glands. It is believed that the cause of the circulatory collapse is the effect of the bacterial poisons on all the tissues of the body. In this the adrenal glands play a part but only a part; they are not wholly responsible for the collapse. It is suggested that in addition to the toxic effect of the poisons and the diminution of the adrenal hormone supply a depletion of vitamin C may be a factor.

The theory is advanced that the changes in the adrenal glands can be accounted for as follows: The increased demand on the adrenal glands, as a result of the infection, depletes the cortical cells of their lipoid (hormone-containing) material; the cells degenerate more rapidly than normally, producing the "tubular" pattern in the outer layers and more conspicuous lesions in the inner layers, with eventual lysis of many of the cells before they have reached their usual site of death; this stage is considered reversible. Later, as a result of the loss of support of the sinusoids because of the premature death of the cortical cells, rupture and hemorrhage may occur—an irreversible stage. The patient may die before hemorrhage occurs.

The primary aim of treatment is to overcome the infection. In addition to the supportive measures usually advocated, it is suggested that, on theoretic grounds, ascorbic acid might be of benefit.

APPENDIX

DETAILS OF THERAPY

CASE 1.—No details on record.

CASE 2.—Penicillin: 30,000 units at 10 a. m., 100,000 units by intravenous drip at 10:30 a. m. and 20,000 units at 1:30 p. m. on January 23.
Sulfadiazine: 4 Gm. by mouth at 6:30 and 9:45 a. m. and 3 Gm. intravenously at 1:30 p. m. on January 23.
Adrenal cortex extract: 20 cc. at 10:30 a. m. on January 23.

CASE 3.—Sulfadiazine: 5 Gm. intravenously at 1 p. m. on March 13.
Adrenal cortex extract: 30 cc. at 1 and 10 cc. at 1:30 p. m. on March 13.
Epinephrine hydrochloride, aqueous solution (1:1,000): 1 cc. at 2:06 p. m. on March 13.

CASE 4.—Penicillin: 40,000 units at 9:30 a. m., 100,000 units at 10:15 a. m. and 25,000 units at 4 p. m. on March 29; 25,000 units at 12, 12:45 and 3 a. m. on March 30, and thereafter every 3 hours day and night until 6 a. m. on April 3.

Sulfadiazine: 7 Gm. intravenously at 9:15 a. m. on March 29; 2 Gm. at 4 p. m. and 1 Gm. intravenously at 7:45 p. m. on March 30; 2 Gm. subcutaneously at 12 and 4 a. m. and 1.5 Gm. by mouth at 10 a. m. and 6 p. m. on March 31; 1.5 Gm. at 2 a. m. on April 1, and thereafter 1.5 Gm. every 4 hours, day and night until 4 p. m. on April 15.

Adrenal cortex extract: 30 cc. at 8:30 a. m., 10 cc. at 9:30 and 11 a. m. and at 2, 8 and 11 p. m., and 6 cc. at 5 p. m. on March 29; 10 cc. at 5 and 11 a. m. and 2 and 5 p. m. on March 30 and 31 and April 1, and beginning at 2 a. m. on April 2, 10 cc. every 4 hours, day and night until April 7.

Desoxycorticosterone: 10 mg. at 10:30 a. m. on March 29.

Epinephrine hydrochloride, aqueous solution (1:1,000): 1 cc. at 8:50 and 9:15 a. m. and 2:15 and 4:50 p. m. on March 29 and 0.5 cc. intravenously at 12 a. m. on March 30.

Epinephrine in oil (1:500): 1 cc. at 11 a. m. on March 29 and 1 cc. at 12:10 a. m. and 4 and 6 p. m. on March 30.

Plasma: 500 cc. at 11:40 a. m. on March 29.

CASE 5.—Penicillin: 40,000 units at 8:45 a. m., 100,000 units intravenous drip at 10 a. m. and 25,000 units at 3, 6 and 9 p. m. on April 14, and 25,000 units at 12, 3, 6 and 9 a. m. and 12, 3 and 6 p. m. on April 15.

Sulfadiazine: 5 Gm. intravenously at 6 p. m. and 2.5 Gm. subcutaneously at 8:30 p. m. on April 13, 2.5 Gm. subcutaneously at 4:30 a. m. and 2 Gm. intravenously at 9 a. m. on April 14.

Adrenal cortex extract: 30 cc. at 8:30 a. m. and 10 cc. at 10:30 a. m. and at 12:30, 3:30 and 5 p. m. on April 14, then every 2 hours, day and night through 7 p. m. on April 15.

Desoxycorticosterone: 10 mg. at 8:50 a. m. and 5 mg. at 10:30 a. m. on April 14.

Epinephrine hydrochloride, aqueous solution (1:1,000): 0.5 cc. at 9 a. m. on April 14.

Epinephrine in oil (1:500): 1 cc. at 12 and 7 p. m. on April 14 and at 3 and 11 a. m. and 7 p. m. on April 15.

Plasma: 250 cc. at 6 p. m. on April 15.

CASE 6.—Penicillin: 25,000 units at 11 a. m. and 12 p. m. and 40,000 units at 3, 6 and 9 p. m. on December 4; 40,000 units every 3 hours, day and night, beginning at 12 a. m. on December 5 and continuing through 9 a. m. on December 9; intrathecally, 10,000 units at 9:30 a. m. on December 5, and 7,000 units at 8:45 a. m. on December 6.

Sulfadiazine: 4 Gm. intravenously at 2 p. m., 2 Gm. intravenously at 6 p. m. and 1 Gm. subcutaneously at 10 p. m. on December 4; 1 Gm. at 2 a. m. on December 5; then 1 Gm. every 4 hours, day and night, until 10 a. m. on December 7, and then 1 Gm. every 6 hours until 8 a. m. on December 10.

Adrenal cortex extract: 2 cc. intravenously at 2:30 p. m. on December 4.

Epinephrine hydrochloride, aqueous solution (1:1,000): 1 cc. at 2:15 p. m. on December 4.

Epinephrine in oil (1:500): 1 cc. at 2:45, 4:30 and 8 p. m. on December 4 and at 4:30 a. m. on December 5.

Plasma: 500 cc. at 3:15 p. m. on December 4.

Insulin: 10 units at 5:10, 8 and 11 p. m. on December 4; at 5 a. m. and 3:45 p. m. on December 5, and at 1:30 and 5 p. m. on December 6.

RHEUMATIC FEVER IN NAVAL ENLISTED PERSONNEL

II. Effectiveness of Intensive Salicylate Therapy in Cases of Acute Infection

COMMANDER R. C. MANCHESTER (MC), U.S.N.R.

ACUTE rheumatic fever in young adults either in naval service [1] or in civilian life [2] begins primarily as an acute infection exhibiting acute polyarticular arthritis as the major manifestation. The disabling character of the acute polyarticular manifestations results in early medical care in most instances, before irreparable visceral damage necessarily occurs or the chronicity of infection becomes fixed. Therefore, a therapeutic regimen which succeeds in modifying the natural course of the disease offers the opportunity of preventing these unfortunate sequelae. This paper deals with the effectiveness of intensive salicylate therapy by the Coburn technic [3] in accomplishing these objectives.

The essential problems in the treatment of acute rheumatic fever are: the alleviation of acute articular, visceral and toxic manifestations; the prevention, or lessening of the degree, of permanent cardiac damage; the shortening of the over-all period of active infection and the prevention of relapses and residual chronic infection.

While there is no question that salicylates dramatically relieve the acute articular and toxic manifestations, most observations indicate that the benefits observed are due solely to the peculiar analgesic and antipyretic properties of salicylates rather than to a specific modifying effect on the course of the disease.[4]

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

1. Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel: I. An Analysis of the Major Manifestations Observed, the Factors Involved in Its Occurrence and the Cardiac Residua, Arch. Int. Med. **77**:317-331 (March) 1946.

2. Cohn, A. E., and Lingg, C.: The Natural History of Rheumatic Cardiac Disease, J. A. M. A. **121**:1-8 (Jan. 2) 1943.

3. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: Rational Technique, Bull. Johns Hopkins Hosp. **73**:435-464 (Dec.) 1943.

4. (*a*) Hanzlik, P. J.: Action and Uses of Salicylates and Cinchophen in Medicine, Medicine **5**:197-371 (Aug.) 1926. (*b*) Swift, H. F.: Rheumatic Fever,

(Footnote continued on next page)

Master and Romanoff [4d] compared 33 patients with acute rheumatic fever who received 8 to 10 Gm. of sodium salicylate daily with 30 patients who received no antirheumatic drugs. The incidence and the degree of visceral manifestations and permanent cardiac damage were identical in the two groups. Polycyclic relapses occurred as frequently in one group as in the other, and the duration of active infection was uninfluenced.

Swift [4b] observed that subcutaneous nodules may appear continuously in patients receiving "maximum salicylate dosage." On the basis of biopsy studies of periarticular tissue,[5] he concluded that salicylates tend to control the acute exudative joint and periarticular tissue reactions but fail to suppress the submiliary proliferative lesions characteristic of the less acute phase and responsible for much of the permanent cardiac damage.

Coburn's [3] recent results utilizing intensive salicylate therapy are diametrically opposed to the preceding observations. Patients with acute rheumatic fever were given 10 Gm. or more of sodium salicylate daily, either intravenously for seven to fourteen days followed by oral therapy or orally throughout the course of treatment. Treatment was continued until the blood sedimentation rate had remained normal for a period of two weeks. In none of a group of 38 patients treated by this method did valvular heart disease develop, while in 20 of 63 patients receiving only symptomatic therapy there developed physical signs of heart disease. In addition, the duration of active infection and the incidence of polycyclic relapses were materially reduced. Coburn expressed the opinion that plasma salicylate levels of 35 mg. per hundred cubic centimeters or higher will suppress rheumatic infection, prevent significant cardiac residua and shorten the duration of active infection.

CLINICAL MATERIAL AND METHODS

The group for study comprised 77 young men afflicted with acute rheumatic fever, all of whom exhibited acute polyarticular arthritis as the major incipient manifestation. Each patient exhibiited a temperature of 100 F. or over and had acute articular and/or visceral manifestations when therapy was instituted in this hospital. Therefore, the less severe, spontaneously subsiding infections have, for the most part, been excluded.

The elapsed time between the onset of the acute illness and the institution of treatment in this hospital was from one to five days in 30 per cent, five to ten

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Am. J. M. Sc. **170**:631-647 (Nov.) 1925. (*c*) Murray-Lyon, R. M.: Salicylates in Rheumatic Fever, Edinburgh M. J. **43**:84-89 (Feb.) 1936. (*d*) Master, A. M., and Romanoff, A.: Treatment of Rheumatic Fever Patients With and Without Salicylates: Clinical and Electrocardiographic Study, J. A. M. A. **98**:1978-1980 (June 4) 1932.

5. Swift, H. F.: Pathogenesis of Rheumatic Fever, J. Exper. Med. **39**:497-508 (April) 1924.

days in 31 per cent, ten to fifteen days in 25 per cent and fifteen to twenty-five days in 14 per cent. Ninety per cent of the patients were classified as having new infections and 5 per cent as having polycyclic recrudescences because of an antecedent attack within a period of one year, and 5 per cent had suffered from recurrent rheumatic fever with residual chronic pain in the joints between the acute attacks.

Fifty-four patients received intensive salicylate therapy patterned after the regimen laid down by Coburn.[8] To 35 of them 10 Gm. of sodium salicylate in 1 liter of lactate Ringer solution or isotonic solution of sodium chloride was administered daily for four to ten days, followed by oral therapy. Nineteen additional patients received oral therapy throughout the course of treatment. Intravenous medication was begun at 9 a. m. and completed at 3 p. m., requiring six hours for administration. Oral medication consisted of from 10 to 12 Gm. of acetylsalicylic acid or sodium salicylate daily, usually in conjunction with 8 Gm. of sodium bicarbonate. It was given in equally divided doses each four hours and was continued until the erythrocyte sedimentation rate had been within normal limits for two weeks.

Twenty-three patients who received small quantities of salicylates for symptomatic relief of acute symptoms comprised the control group. In most instances those who exhibited prolonged infection received intensive therapy late in the course of observation.

The duration of active infection was based on the erythrocyte sedimentation rate, an oral temperature over 99 F., a shifting P-R interval of over 0.2 second and clinical evidence of active articular and visceral manifestations.

Cardiac murmurs were recorded as very slight, slight, moderate and loud. Mitral systolic murmurs were evaluated with the patient in the horizontal position and lying on the left side. Under these conditions, slight mitral systolic murmurs transmitted to or beyond the anterior axillary line may be expected in 4 per cent of healthy service personnel and murmurs of moderate intensity are not observed.[1] Data for patients with preexisting heart disease have been excluded.

Electrocardiograms were taken at weekly intervals. Deviations from normal were based on the criteria adopted by the American Heart Association. Erythrocyte sedimentation rates were determined twice weekly by the Cutler technic.

Patients were kept under observation in this hospital until the rheumatic infection was quiescent or until chronic infection had persisted for more than three months. The shortest period of observation was twenty-seven days, the longest two hundred and eighty-four days and the average sixty-six days.

RESULTS OF TREATMENT

A comparison of the results obtained in the intensively treated and in the control group has been made on the basis of temperature, articular manifestations, erythrocyte sedimentation rate, electrocardiographic and cardiac responses and the incidence of relapses and residua.

The temperature and articular responses are presented in table 1.

The average duration of fever was 2.6 days and of objective articular manifestations 2.8 days in the 54 patients receiving intensive therapy. The longest period of fever in any patient was eight days and of objective articular manifestations six days. Treatment was

equally effective whether instituted early or late in the first twenty-five days of acute illness. In striking contrast, average duration of fever in the control group was fifteen days and of objective articular manifestations twenty-six days. Fever recurred for sixty days and objective articular manifestations for one hundred and fifty-four days in 1 patient and articular manifestations for eighty days in another. Intensive

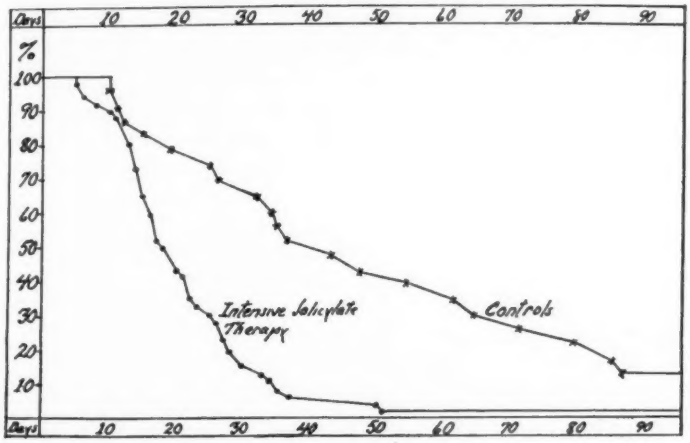

Chart 1.—The duration of elevated erythrocyte sedimentation rate in patients receiving intensive salicylate therapy and in the control group.

intravenous and oral therapy instituted late in these refractory cases was not particularly effective.

Erythrocyte sedimentation rate responses are represented graphically in chart 1. The erythrocyte sedimentation rate remained elevated for

TABLE 1.—*The Average Duration in Days of Fever and of Objective Articular Manifestations in the Intensively Treated and in the Control Group*

	Number of Cases	Average Duration in Days	
		Fever	Objective Articular Manifestations
Intensive salicylate therapy	54	2.6	2.8
Controls	23	15	26

more than ninety days in only 1 patient, or 2 per cent, of the group receiving intensive salicylate therapy, in contrast to a persistent elevation observed in 13 per cent of the control group. Excluding these patients, the average duration of elevated erythrocyte sedimentation rate was twenty days in the intensively treated patients and forty-two days in the controls. As shown in table 2, intensive therapy was

equally effective whether instituted early or late in the first twenty-five days of the acute illness.

Of the 54 patients receiving intensive therapy, treatment was instituted with salicylates intravenously followed by oral therapy for 35, while 19 received oral therapy throughout the entire course of

TABLE 2.—*Comparison of the Effectiveness of Intensive Therapy in Relation to the Duration of Elapsed Illness Before Treatment was Instituted*

Duration of Acute Illness	Number of Cases	Average Duration in Days		
		Fever	Objective Articular Manifestations	Elevated Erythrocyte Sedimentation Rate
1- 5 days	16	2.7	2.8	19
5-10 days	14	2.4	2.7	21*
10-15 days	16	3.2	3.6	22
15-25 days	8	2.0	2.7	20

* One patient with persistent elevation of the erythrocyte sedimentation rate is excluded.

treatment. A comparison of the effectiveness of the two therapeutic regimens in alleviating fever and objective articular manifestations and suppressing elevation of the erythrocyte sedimentation rate is presented in table 3. The average duration of elevated erythrocyte sedimentation rate was twenty days, whether salicylate therapy was instituted intravenously or orally, while fever lasted a day longer and objective articular manifestations 1.1 days longer in the orally treated group. One patient started on intravenous therapy required 20 Gm. on the second and third days for complete relief of fever and articular signs.

TABLE 3.—*Effectiveness of Regimens Instituted by the Intravenous Route and of Those Consisting Entirely of Oral Therapy in Alleviating Fever, Objective Articular Manifestations and Elevated Erythrocyte Sedimentation Rate*

Administration of Salicylate	Number of Cases	Duration in Days		
		Fever	Objective Articular Manifestations	Elevated Sedimentation Rate
Intravenous followed by oral therapy	35	2	2.5	20
Oral therapy only	19	3	3.6	20

Three patients had recurrences of objective articular manifestations, and 1 other had a recurrence of fever and an increase in pericardial effusion after he was changed to oral therapy. Symptoms and signs promptly subsided in the former 3 patients with another course of salicylates intravenously. The latter patient was given 6 Gm. of aminopyrine daily instead of further salicylates intravenously, in order to avoid the excessive respiratory stimulation which often occurs in

patients with cardiac dyspnea.[6] The acute symptoms promptly subsided and did not recur on subsequent salicylate therapy. This evidence in conjunction with clinical observations is interpreted as indicating that intensive regimens instituted orally are as effective in most instances as those utilizing salicylates intravenously but that in cases of severer refractory infections salicylates administered intravenously are required.

Signs of recognizable cardiac involvement in acute rheumatic fever consist of cardiac murmurs, clinical and roentgenologic evidence of enlargement, certain arrhythmias, electrocardiographic abnormalities, gallop rhythms and evidence of pericarditis. Slight and moderate mitral systolic murmurs, electrocardiographic abnormalities and pericardial friction rubs without effusion reflect incipient recognizable carditis which may or may not develop into a significant degree of cardiac damage. These signs were classified in this study as signifying "potential rheumatic heart disease." Diastolic and loud systolic murmurs, clinical and roentgenologic evidence of cardiac enlargement, gallop rhythms and pericardial effusion signify a serious degree of cardiac damage. They were classed as indicating "significant carditis" in the presence of active infection and as indicating "significant cardiac residua" after all evidence of active infection had subsided.

Levy and Turner[7] found that salicylates hastened the recession of abnormal electrocardiographic tracings in rheumatic fever, while Carr and Reddick[8] and Wyckoff, DeGraff and Parent[9] observed that doses of salicylates as high as 8 Gm. daily were ineffective.

In this study 35 per cent of the patients receiving intensive salicylate therapy and 40 per cent of the controls exhibited electrocardiographic abnormalities. In chart 2 is presented graphically the duration of these abnormalities. On comparison of results in the two groups, it is apparent that electrocardiographic abnormalities subsided more rapidly in patients receiving intensive salicylate therapy than in the others, but the difference was not striking.

The cardiac manifestations at the termination of treatment in this hospital are presented in table 4. Of those patients who received

6. Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel: III. The Physiologic and Toxic Effects of Intensive Salicylate Therapy, J. A. M. A. **131**:209-213 (May 18) 1946.

7. Levy, R. L., and Turner, K. B.: Variations in Auriculo-Ventricular Conduction Time in Rheumatic Carditis with Salicylate Therapy, Proc. Soc. Exper. Biol. & Med. **25**:64 (Oct.) 1927.

8. Carr, J. G., and Reddick, W. G.: Conduction Disturbances in Acute Rheumatic Infections, J. A. M. A. **91**:853-856 (Sept. 22) 1928.

9. Wyckoff, J.; DeGraff, A. C., and Parent, S.: The Relationship of Auriculoventricular Conduction Time in Rheumatic Fever to Salicylate Therapy, Am. Heart J. **5**:568-573 (June) 1930.

intensive therapy, 71 per cent showed no residual cardiac stigmas; 15 per cent were classified as having potential rheumatic heart disease on the basis of a slight or moderate mitral systolic murmur; 7.4 per cent had had significant carditis when treatment was instituted, which cleared up completely, except in 1 patient who was left with a moderate mitral systolic murmur and was classed as having potential rheumatic

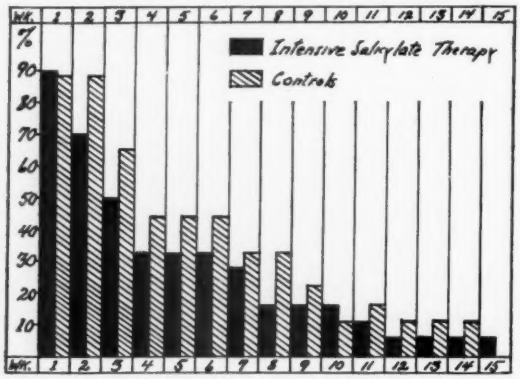

Chart 2.—The duration of abnormal electrocardiographic manifestations in patients of the intensively treated group and of the control group who exhibited such changes.

TABLE 4.—*The Cardiac Status of the Intensively Treated Group and of the Control Group at the Time of Discharge From This Hospital*

	Cardiac Status at Discharge					
			Significant Carditis Clearing Up to			
Therapy	Normal Heart, per Cent	Potential Rheumatic Heart Disease, per Cent	Potential Heart Disease, per Cent	Normal, per Cent	Significant Cardiac Residua, per Cent	Cardiac Deaths, per Cent
Intensive salicylate therapy	71	13	1.9	7.6	7.4	1.9
Control group	48	39	...	4.3	13	...

heart disease; 7.4 per cent suffered significant cardiac residua, and 1.9 per cent, or 1 patient, died of heart disease. The last patient had exhibited severe pancarditis and heart failure on admission and died on the fourth day of treatment. Significant carditis did not develop in a single patient who had not shown evidence of it before treatment was begun.

These results are in striking contrast to those in the control group, only 48 per cent of whom escaped with normal hearts. Thirty-nine per cent were classified as having potential rheumatic heart disease;

4.3 per cent had had significant carditis which cleared up and 13 per cent exhibited significant cardiac residua. Among the 3 patients with significant cardiac residua, only 1 showed evidence of cardiac involvement on admission to this hospital. It developed in the other 2 while they were under observation. In contrast, in none of the patients receiving intensive therapy did significant carditis develop after treatment was instituted.

TABLE 5.—*Cardiac Observations on Admission and at Discharge From This Hospital in Those Patients Who Exhibited Evidence of Significant Carditis*

Group	Patient	Cardiac Observations on Admission	Cardiac Observations at Discharge
Intensive salicylate therapy	V. M. A.	Massive pericardial effusion; electrocardiogram positive	First degree cardiac enlargement; moderate mitral systolic murmur transmitted to axilla
	C.	Massive pericardial effusion; electrocardiogram positive	Loud aortic diastolic murmur, moderately loud mitral systolic murmur transmitted to axilla; heart not enlarged
	D.	First degree cardiac enlargement; loud mitral systolic murmur transmitted to axilla; electrocardiogram positive	Loud mitral systolic murmur transmitted to axilla; no cardiac enlargement
	R. J. D.	Slight aortic diastolic murmur; loud mitral systolic murmur transmitted to axilla; electrocardiogram positive	Loud mitral systolic murmur transmitted to axilla; no cardiac enlargement
	N. D. E.	First degree cardiac enlargement; moderately loud systolic murmur transmitted to axilla; electrocardiogram positive	Moderate systolic murmur transmitted to axilla; no cardiac enlargement
	S. R. O.	Slight aortic diastolic murmur; moderate mitral systolic murmur	Normal
	C. D. E.	First degree cardiac enlargement	Normal
	B.	First degree cardiac enlargement; electrocardiogram positive	Normal
Control group	W. O. V.	Normal	Second degree cardiac enlargement; loud aortic diastolic murmur; loud mitral systolic murmur transmitted to axilla
	G. J. W.	Slight mitral systolic murmur; electrocardiogram positive	Loud mitral systolic murmur transmitted to axilla; middiastolic mitral murmur
	M. W. H.	Loud mitral systolic murmur transmitted to axilla; first degree cardiac enlargement	Loud mitral systolic murmur transmitted to axilla; moderate cardiac enlargement
	I. J. B.	Electrocardiogram positive; first degree cardiac enlargement after admission	Normal

Fifteen per cent of those receiving intensive therapy and 9 per cent of the controls exhibited significant carditis before treatment was begun in this hospital. Yet at the end of treatment the percentage was reversed, with only 7.4 per cent of the intensively treated patients suffering from significant residua in contrast to 13 per cent of the control group. An analysis of the cardiac observations on admission and on discharge is presented in table 5. Carditis progressed in the early phase of intensive therapy in some instances, but thereafter the

cardiac course was one of gradual improvement, and none of the patients suffered from progressive damage. Therefore the conclusion seems justified that already existing carditis was favorably influenced.

Two deaths occurred in the group of 54 patients receiving intensive therapy, while there were no fatalities in the control group. One death occurred on the fourth day, due to acute fulminating pancarditis. The other occurred on the seventh day, as a result of extensive rheumatic pneumonitis. The absence of fatalities in the 23 controls does not reflect dangers inherent in intensive salicylate therapy but, rather, reflects the fact that patients with milder disease were selected for the control group.

Polycyclic recrudescences of infection occur in between 20 per cent and somewhat under 50 per cent of young adults suffering from acute polyarticular rheumatic fever treated by rest in bed and sedation without antirheumatic drugs.[10] In addition, the incidence of cardiac and other visceral manifestations increases with each relapse.[10a] While recrudescences occurred in 22 per cent of the controls, the incidence was only 7.4 per cent in the 54 patients receiving intensive therapy. Only 1 of the 4 patients comprising the latter group showed an elevated erythrocyte sedimentation rate during the relapse. In none of them did recognizable cardiac or visceral manifestations develop, and their symptoms were promptly relieved by the resumption of salicylate therapy. The 22 per cent who exhibited recrudescences in the control group presented a less favorable picture. One had associated evidence of acute nephritis; one suffered from additional acute cardiac damage, and all 5 exhibited an elevation in the erythrocyte sedimentation rate.

The recognition of chronic residual infection presents a difficult problem. Subjective arthralgias and cardiac residua do not necessarily indicate active infection. In addition, systemic reactions to rheumatic infection are apparently modified in the intensively treated patients, as reflected by the fact that the erythrocyte sedimentation rate was elevated in only 1 of the 4 patients exhibiting polycyclic recrudescences while it was elevated in each of the 5 in the control group showing relapses.

Fifteen per cent of the patients receiving intensive therapy suffered from residual subjective arthralgias. One of these showed persistent elevation of the erythrocyte sedimentation rate, while 2 others suffered from pains in the joints of sufficient severity to indicate that active infection still existed. None of the 7.4 per cent exhibiting significant

10. (*a*) Graef, I.; Parent, S.; Zitron, W., and Wyckoff, J.: Studies in Rheumatic Fever: I. The Natural Course of Acute Manifestations of Rheumatic Fever Uninfluenced by "Specific Therapy," Am. J. M. Sc. **185**:197-210 (Feb.) 1933. (*b*) Master and Romanoff.[4d]

cardiac residua showed evidence of chronic active infection, nor did they complain of residual arthralgias.

Twenty-six per cent of the control group complained of residual subjective arthralgias, with the erythrocyte sedimentation rate remaining elevated in 3 instances. One of these showed progressive cardiac damage in conjunction with chronic arthralgia, even after the erythrocyte sedimentation rate had returned to normal on the one hundred and twelfth day. None of the others exhibited significant cardiac residua, nor did any with significant cardiac residua exhibit chronic arthralgias except in the case mentioned. On the basis of the evidence presented, the incidence of chronic infection was regarded as 5 per cent in the intensively treated group and as 18 per cent in the controls. Furthermore, no relationship was found between chronic residual arthralgias and cardiac involvement. Chronic arthralgias do not in themselves reflect active infection, nor do they lead to rheumatic heart disease.

COMMENT

The clinical material presented clearly indicates that intensive salicylate therapy instituted in the first twenty-five days of the acute illness in young adults successfully suppresses rheumatic infection. Acute articular and toxic manifestations are dramatically relieved. Significant cardiac residua are prevented if therapy is instituted before significant signs of carditis have appeared. Already existing carditis is favorably influenced. The period of active infection is materially shortened, and polycyclic recrudescences and residual chronic infection, although not prevented, occur less frequently in patients receiving intensive salicylate therapy than in those receiving symptomatic therapy.

Oral therapy is as effective in most instances as treatment administered by the intravenous route. Nevertheless, salicylates given intravenously are more effective in controlling severe and more refractory infections and are required in such cases. Fulminating infections do not always respond favorably. Thus, 1 patient with extensive rheumatic pneumonitis and another with acute pancarditis died shortly after treatment was begun. In 2 others receiving salicylates intravenously, resort to pericardial paracentesis for relief of effusion was not avoided. The preponderance of evidence, nevertheless, indicates that already existing significant carditis is favorably influenced.

The patients included in this study represent a group from whom persons with milder spontaneously subsiding infections have, for the most part, been excluded. If such persons are added, the 7.4 per cent incidence of significant cardiac residua in the intensively treated group would be even lower. Likewise, the effectiveness of intensive salicylate therapy, as reported in this study, applies only to those patients for

whom treatment was instituted within the first twenty-five days of the acute illness. Experience with patients with chronic rheumatic fever and with patients treated late in their illness has been far less favorable.

Chronic arthralgias, as an isolated symptom, do not reflect active rheumatic fever. No relationship was observed between chronic arthralgia and cardiac involvement, and those patients who exhibited residual arthralgias were remarkably free from heart disease. Therefore, the persistence of low grade arthralgias without other evidence of active infection does not dictate the restriction of physical activity as a prophylaxis against cardiac complications.

Accepting the value of Coburn's intensive salicylate regimen in cases of acute rheumatic fever, the problem of its safe yet effective application remains to be considered. These factors are discussed in a subsequent paper.[6]

CONCLUSIONS

1. Intensive salicylate therapy suppresses rheumatic infection in the acute stages occurring in young adults when treatment is instituted within twenty-five days after inception of the acute infection.

2. Acute articular and toxic manifestations are dramatically relieved.

3. Significant cardiac residua are prevented if therapy is instituted before signs of significant carditis have appeared. Already existing acute carditis is favorably influenced, although residual stigmas are not necessarily prevented.

4. The period of active infection is materially shortened, and relapses and residual chronic infection, although not prevented, occur less frequently in patients receiving intensive salicylate therapy than in those receiving symptomatic therapy.

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CHANGES IN HEMOGLOBIN AND TOTAL PLASMA PROTEIN AFTER INJECTION OF MERCUROPHYLLINE

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SINCE Saxl and Heilig [1] introduced the organic mercurial diuretics into the treatment of cardiac edema, many studies have been reported concerning their mechanism of action. The renal action of these diuretics has been proved by experiments on the isolated heart-lung-kidney preparation (Gremels [2]) and by observations on transplanted kidneys (Govaerts [3]). Investigations using the creatinine clearance method on dogs (Schmitz [4]) and on men (Herrmann and his colleague [5]) showed that the administration of these diuretics effected a diminished tubular reabsorption.

Evidence for an extrarenal action of the organic mercurial diuretics has also been brought forward, but is less convincing. The method usually employed when this problem of renal as against extrarenal action of mercurial diuretics is investigated is to examine the fluctuations in hemoglobin content or hematocrit values, total plasma protein and plasma volume during diuresis. It is reasoned that a primary extrarenal action of these drugs, effecting a transfer of tissue fluids to the blood stream, will result in a temporary hydremia, i. e., an increase in plasma volume, with a fall in hemoglobin and plasma protein. On the other hand, a preponderantly or exclusively renal action will cause hemoconcentration.

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Contradictory findings (i. e., hemoconcentration and hemodilution) have been reported by different investigators, and these have been interpreted as arguments for either of the two theories of the site of action of the mercurial diuretics.

It was the purpose of the present investigation to study some factors which might explain the variability of the changes in the hemoglobin and total plasma protein due to the administration of the mercurial diuretics. It will be shown that, whereas the time at which the blood is examined after the injection of the mercurial diuretics is of minor importance, the presence or absence of peripheral edema is a decisive factor in determining the direction of the changes in hemoglobin and plasma protein during diuresis.

MATERIAL AND METHODS

Fluctuations in hemoglobin and total plasma protein were studied in 34 patients during the diuresis following injection of mercurophylline. Of these patients 23 had congestive heart failure, 8 had cirrhosis of the liver in the state of decompensation and 2 had carcinomatosis of the peritoneum with ascites. The congestive heart failure was due to rheumatic heart disease in 14 cases, to hypertension and arteriosclerosis in 7 and to ephysema of the lungs in 2. Repeated mercurophylline injections (two to four) were given to 13 patients and the resulting blood changes studied, so that altogether 57 experiments were performed.

In 29 instances the patients had peripheral edema at the time of the experiment. Twenty of these patients had heart failure, 8 cirrhosis of the liver and 1 carcinomatosis of the peritoneum. In the other 28 instances no peripheral edema was present at the time at which the mercurial diuretic was given the patients.

Six patients with heart failure were investigated at a time when they exhibited peripheral edema and again at a later date when it was absent.

Prior to the injection of mercurophylline all patients were kept in bed for several days on restricted fluids and a diet low in salt. After two days of preparatory treatment with ammonium chloride (3 to 5 Gm. daily) mercurophylline (1 to 2 cc.) was injected intravenously. The quantity of fluids allowed during the twenty-four hours following injection varied from 600 to 1,000 cc. The body weight was recorded immediately before and twenty-four hours after injection. The quantity of urine produced between the times of blood sampling was measured. Estimations of hemoglobin and plasma—or of serum protein—were made at the time of injection of the diuretic and repeated within each of the following periods: one to seven hours, seven to thirteen hours and seventeen and one-half to twenty-eight hours after injection. Blood

estimations within the one to seven hour period were performed in a limited number of cases only. All blood samples were taken before meals. They were obtained by venipuncture, without stasis. Hemolyzed blood was discarded.

In the cases designated by "K. H." (column "method" of table 1), the specific gravity of the serum was determined by the falling drop method of Kagan.[6] The protein values were calculated from the specific gravity using the formula of Kagan.[7] The blood hemoglobin content was determined using the method of Heilmeyer[8]: 0.2 cc. of oxalated blood was diluted with 9.8 cc. of 0.4 per cent solution of ammonia, and a knife point of sodium thiosulfate was added. Colorimetric readings were taken with the Pulfrich *Stufen* photometer. If duplicate values differing by more than 3 per cent were obtained, additional determinations on the same blood sample were made. The extinction factor used was 0.92.[8]

In the cases marked with "C" (table 1, column "method"), the cupric sulfate method of Phillips and his colleagues[9] was used to determine the specific gravity of whole blood and plasma. The set of cupric sulfate solutions differing in specific gravity by 0.0001 was employed. Hemoglobin and plasma protein values were calculated according to the nomograph given by the authors.

RESULTS

The results of the observations are arranged in tables 1 and 2. In table 1 the cases in which there was edema are recorded. In table 2 the cases in which there was not edema are recorded.

The changes observed one to seven hours after injection of the diuretic ranged for hemoglobin from — 8.5 per cent to + 19.5 per cent and for total plasma protein from — 4.1 per cent to + 25.1 per cent.

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TABLE 1.—*Instances in Which Patients Had Peripheral Edema*

Number	Initials	Failure of Left Side of Heart	Peripheral Edema	Enlargement of Liver	Ascites	Mercurophylline Cc.	Method	At the Time of Injection: Hemoglobin Gm. per 100 Cc.	At the Time of Injection: Protein Gm. per 100 Cc.	At the Time of Injection: After Hours	Within 1-7 Hours After Injection: Percentage Change* Hemoglobin	Within 1-7 Hours After Injection: Percentage Change* Protein	Within 1-7 Hours After Injection: Diuresis Total Cc.	Within 1-7 Hours After Injection: Diuresis Cc. Min.	Within 7-13 Hours After Injection: After Hours	Within 7-13 Hours After Injection: Percentage Change* Hemoglobin	Within 7-13 Hours After Injection: Percentage Change* Protein	Within 7-13 Hours After Injection: Diuresis Total Cc.	Within 7-13 Hours After Injection: Diuresis Cc. Min.	Within 17½-28¾ Hours After Injection: After Hours	Within 17½-28¾ Hours After Injection: Percentage Change* Hemoglobin	Within 17½-28¾ Hours After Injection: Percentage Change* Protein	Within 17½-28¾ Hours After Injection: Diuresis Total Cc.	Within 17½-28¾ Hours After Injection: Diuresis Cc. Min.	Loss of Wt. Kg.
Diagnosis: Cirrhosis of the Liver																									
1	B. Ts	..	+	+	+	2	K. H.	11.3	6.44	4.15	— 8.5	....	.....	....	8	....	— 8	.....	....	24	— 5.3	— 8	2,100	1.46	1.4
2	E. S.	.	+	—	+	2	C.	13.3	7.0	....	....	....	.....	....	11	— 2.3	— 3.3	800	1.21	24	+ 4.2	— 1.5	1,250	0.87	0.4
3	E. S.	..	+	+	+	2	C.	11.8	6.2	....	....	....	.....	....	8	— 2.6	— 4.8	600	1.25	18	0	0	800	0.74	0.2
4	E. S.	..	+	—	+	2	C.	12.6	6.55	....	....	....	.....	....	10	— 4.8	— 5.3	2,140	3.57	24	— 4.8	— 3.8	2,990	2.08	1.9
5	E. S.	..	+	—	+	2	C.	12.4	6.0	....	....	....	.....	....	9	0	0	1,710	3.17	21	— 1.5	0	2,100	1.67	1.2
6	G. A.	..	+	—	+	2	K. H.	14.75	4.98	....	....	....	.....	....	8.35	— 4	+ 1	2,500	4.85	24	— 4.0	0	2,720	1.89	2.3
7	G. A.	..	+	+	+	2	K. H.	12.0	4.69	....	....	....	.....	....	7.30	— 3.3	+ 2.5	2,410	5.35	21.30	— 3.3	+ 3.5	5,510	4.27	5.5
8	Sh. B.	..	+	—	+	2	K. H.	.....	4.0	1	....	+ 8.5	.....	....	7.30	....	+16.5	.....	....	24	....	....	3,400	2.36	...
Diagnosis: Heart Failure; Rheumatic Heart Disease																									
9 (50-51)†	A. C.	+	+	+	+	2	C.	14.7	7.2	....	....	....	.....	....	11	— 4.8	— 7	1,000	1.51	26.30	— 2	— 9.7	3,400	2.14	3.0
10	A. C.	+	+	+	±	2	C.	14.2	6.6	....	....	....	.....	....	10	+ 2.4	— 6	1,030	1.72	26	+ 4.8	+ 1	2,980	1.91	2
11 (44)	B. G.	+	+	+	—	1.5	C.	14.15	5.78	5.15	0	— 3.3	1,300	4.13	10	— 1	— 6.6	1,990	3.32	23	— 1	— 4.5	2,410	1.75	2.4
12	B. G.	+	+	+	—	2	K. H.	13.8	5.83	5	+ 2.5	+ 6.7	1,925	6.42	11.30	+ 2.5	+ 5.5	2,990	4.33	23.30	+ 3.6	+ 1.7	3,670	2.60	3.4
13 (49)	F. Sch.	+	+	+	—	2	K. H.	13.55	5.92	5	— 1	+ 7.8	1.440	4.80	9	+ 6.3	+17.4	3,000	5.66	23	0	+ 6.5	5,460	3.96	1.4
14	F. B.‡	+	+	—	—	2	K. H.	10.05	6.53	....	....	....	.....	....	10	— 2.5	— 6.1	850	1.42	24	— 2.5	....	.....	....	...
15	A. Ch.	+	+	+	+	2	K. H.	.....	6.69	3.45	....	+ 3.4	.....	....	9.45	....	+ 4.8	.....	....	28.15	....	+ 3.6	3,800	2.24	3.0
16	J. M.	+	+	+	+	2	K. H.	.....	6.13	6	....	+ 0	.....	....	6	....	0	.....	....	24	....	....	4,400	3.06	2.9
17	J. M.	+	+	+	—	2	K. H.	.....	5.82	1	....	— 2.4	.....	....	9	....	+ 3.4	.....	....	24	....	....	2,200	1.53	1.3
Diagnosis: Hypertensive Arteriosclerotic Heart Disease																									
18 (52)	N. B. C.	+	+	+	+	2	C.	15.7	6.8	....	....	....	.....	....	8	— 8.3	— 3	1,300	2.71	21	+ 3.8	+ 7.3	2,500	1.98	2.3
19	N. B. C.	+	+	+	+	2	C.	16.3	7.3	....	....	....	.....	....	12	— 2	0	1,220	1.69	24	— 8	0	2,500	1.74	2.5
20	N. B. C.	+	+	+	—	2	C.	14.9	7.42	....	....	....	.....	....	9	+ 9.4	+ 2.4	1,350	2.50	25	0	— 1	2,500	1.66	2.5
21	Sh. M.	+	+	+	—	1	K. H.	13.7	5.94	....	....	....	.....	....	.....	....	....	.....	....	24	+ 5.1	+ 1.9	960	0.67	...
22	D. S.	+	+	+	—	2	K. H.	16.6	6.78	6.30	0	— 1.5	2,290	5.9	13	— 1.5	+ 3.8	3,060	3.92	24	+ 5.0	+ 5	3,240	2.25	...
23 (53)	E. F.	+	+	+	—	2	K. H.	11.95	5.3	5	0	0	270	0.9	10	— 2.7	0	610	1.02	24	+ 2.5	+ 1.9	1,410	0.98	0.7
24 (54)	J. F.	+	+	+	—	2	K. H.	15.55	5.85	5.30	— 1	— 1.5	1,060	3.21	8.30	0	0	1,610	3.16	24.30	+ 1.0	— 2.5	1,880	1.28	2.2
25	J. K.	+	+	+	+	1	K. H.	10.65	6.02	2.30	— 2.8	— 4.1	.....	....	8	0	0	1,065	2.22	24	— 2.8	0	2,500	1.74	2.5
26	J. K.	+	+	+	—	1	K. H.	11.3	5.96	....	....	....	.....	....	7	0	+ 6.9	.....	....	24	....	....	1,400	0.97	1.9
Diagnosis: Corpulmonale																									
27	A. Sh.	±	+	+	+	2	K. H.	18.5	6.2	....	....	....	.....	....	7.25	— 10	— 9.2	.....	....	22	— 4.9	— 6.4	1,800	1.36	1.1
28	A. G.	±	+	+	+	1.5	K. H.	17.35	5.26	....	....	....	.....	....	7	+ 3.4	....	.....	....	21	+ 4.6	+ 7.6	1,000	0.79	...
Diagnosis: Carcinomatosis of the Peritoneum																									
29	J. B.	..	+	+	+	2	K. H.	10.05	6.43	....	....	....	.....	....	9	+ 6.5	+ 5.9	1,450	2.68	23.30	— 3.8	+ 2.3	3,350	2.38	2.8

* The changes in hemoglobin and in plasma protein are expressed in percentages of the amounts found at the time of the injection of the diuretic. + indicates a rise and — indicates a fall in amount of hemoglobin or plasma protein.

† The numbers in parentheses refer to experiments on the same patient in table 2.

‡ Subacute bacterial endocarditis.

* The changes in hemoglobin and in plasma protein are expressed in percentages of the amounts found at the time of the injection of the diuretic. + indicates a rise and — indicates a fall in amount of hemoglobin or plasma protein.
† The numbers in parentheses refer to experiments on the same patient in table 2.
‡ Subacute bacterial endocarditis.

TABLE 2.—*Instances in Which Patients Were Without Peripheral Edema*

Number	Initials	Failure of Left Side of Heart	Peripheral Edema	Enlargement of Liver	Ascites	Mercurophylline Cc.	Method	At the Time of Injection: Hemoglobin Gm. per 100 Cc.	At the Time of Injection: Protein Gm. per 100 Cc.	At the Time of Injection: After Hours	Within 1-7 Hours After Injection: Percentage Change*: Hemoglobin	Within 1-7 Hours After Injection: Percentage Change*: Protein	Within 1-7 Hours After Injection: Diuresis: Total Cc.	Within 1-7 Hours After Injection: Diuresis: Cc. Min.	Within 7-13 Hours After Injection: After Hours	Within 7-13 Hours After Injection: Percentage Change*: Hemoglobin	Within 7-13 Hours After Injection: Percentage Change*: Protein	Within 7-13 Hours After Injection: Diuresis: Total Cc.	Within 7-13 Hours After Injection: Diuresis: Cc. Min.	Within 17½-28¼ Hours After Injection: After Hours	Within 17½-28¼ Hours After Injection: Percentage Change*: Hemoglobin	Within 17½-28¼ Hours After Injection: Percentage Change*: Protein	Within 17½-28¼ Hours After Injection: Diuresis: Total Cc.	Within 17½-28¼ Hours After Injection: Diuresis: Cc. Min.	Loss of Wt. Kg.
Diagnosis: Cirrhosis of the Liver																									
30	A. R.	..	—	—	+	2	K. H.	14.15	5.43	5	+ 6.7	+ 7.7	.....	....	.....	.....	.....	.....	....	21	....	+ 3.1	4,000	3.18	3.4
31	A. R.	..	—	—	+	2	K. H.	14.45	4.98	6	+ 4.1	+ 9.8	250	0.7	10.30	+ 2.5	+ 9.2	1,560	2.48	24	+11.8	+15.1	4.135	2.87	3.7
32	A. R.	..	—	—	+	1	C.	15.1	5.32	....	.....	.....	.....	....	9.30	+ 1	— 1.1	1,300	2.28	24.30	+ 3.3	+ 0.8	1,650	1.12	1
33	B. M.	..	—	—	+	2	C.	12	6.68	....	.....	.....	.....	....	11	+10	+ 6.1	2,550	3.86	23.30	+ 8.8	+ 8.1	2,950	2.09	2.1
34	F. P.	..	—	—	+	2	C.	12.30	5.44	....	.....	.....	.....	....	9.15	+12.2	+19.9	2.050	3.70	.....	.....	.....	.....	.....	2.4
35	B. J. E.	..	—	—	+	2	K. H.	15.4	5.18	....	.....	.....	.....	....	9	+11.4	+20.6	1,100	2.04	23.30	0	+ 3.3	2,600	1.84	...
Diagnosis: Heart Failure; Rheumatic Heart Disease																									
36	R. A.	+	—	+	—	1.5	C.	11.95	7.2	....	.....	.....	.....	....	12.30	+ 6.6	+ 9.7	1,740	2.32	22.30	.....	.....	2,140	1.59	1.4
37	R. A.	+	—	+	—	1.5	C.	12	7.4	....	.....	.....	.....	....	11.30	+ 6.7	+14	1,750	2.54	24	+ 6.7	+13.5	2,350	1.63	1.7
38	R. A.	+	—	+	—	2	C.	12.2	6.85	....	.....	.....	.....	....	10	+11.5	+21.1	2,310	3.85	24	+13.1	+21.9	3,030	2.14	2.7
39	O. O.	+	—	+	—	2	C.	15.7	6.2	....	.....	.....	.....	....	10	0	— 2.5	.....	.....	24	+10.2	+ 9.7	2,000	1.39	1.5
40	Ch. W.	+	—	+	—	2	K. H.	10	6.05	5.30	+19.5	+25.1	1,550	4.69	10	+18	+20	3,850	6.42	24	+22.0	+20	4,550	3.16	4.9
41	Ch. W.	+	—	+	.	2	K. H.	13.05	7.40	4	— 1.1	— 1	1,025	4.27	9	— 1.1	+ 2	1,325	2.45	23.30	+ 5.7	+ 7.8	2,175	1.54	2.3
42	Ch. W.	+	—	+	—	2	K. H.	9.6	6.33	....	.....	.....	.....	....	11.30	— 2	— 1	810	1.17	23.30	+ 2.5	— 2	1,330	0.94	0.6
43	M. P.	+	—	+	—	2	K. H.	16.95	6.87	....	.....	.....	.....	....	12	— 1	....	1,140	1.58	24	+ 0.6	+ 1.5	1,340	0.93	...
44 (11-12) †	B. G.	+	—	+	—	2	K. H.	13.2	6.35	4.15	+ 3.8	....	1,470	5.18	11	+ 7.2	+ 4.7	2,545	3.86	23.30	+ 7.2	— 1.5	2,785	1.97	2.3
45	A. Ch.	+	—	+	—	2	C.	14.3	7.08	4.30	+ 8.4	+ 5.5	480	1.77	9.15	+11.2	+ 6.9	630	1.14	23.30	+11.2	+ 5.5	980	0.70	0.3
46	S. G.	+	—	+	—	1.5	C.	11.85	6.71	2	— 2	+ 3.9	.....	....	8	+ 1.3	+ 2.2	.....	....	24	+14.3	+20.6	3,150	2.19	2.5
47	J. B.	+	—	+	—	2	K. H.	16.2	6.68	2	0	+ 3.4	340	2.83	7.30	+ 5.6	+15.9	1,360	3.02	25	+ 6.8	+10.8	2,060	1.37	1.6
48	M. K.	+	—	+	—	2	K. H.	16.05	6.27	3	+ 1.9	....	480	2.66	7.30	+ 7.8	+13.7	1,570	3.50	21	+ 9.6	+15.3	2,500	1.98	1.6
49 (13)	F. Sch.	+	—	+	—	2	K. H.	13.2	6.60	2	+ 3.7	+ 3.8	455	3.79	7.30	+ 5.3	+14.2	1,665	3.70	24	0	+10.6	2,245	1.56	2.5
50 (9-10)	A. C.	+	—	+	—	1.5	K. H.	.....	6.17	....	.....	.....	.....	....	.....	.....	.....	.....	....	17.30	.....	+22.7	3,800	3,62	3.4
51	A. C.	+	—	+	—	1.5	K. H.	.....	6.81	....	.....	.....	.....	....	.....	.....	.....	.....	....	21.30	.....	+12.9	3,000	2.33	3.7
Diagnosis: Hypertensive Arteriosclerotic Heart Disease																									
52 (18-19-20)	N. B. C.	+	—	+	—	2	C.	14.7	7.78	....	.....	.....	.....	....	10	+ 7.5	+ 7.9	1,170	1.95	24	+ 4.8	+ 1.3	1,970	1.37	2.5
53 (23)	E. F.	+	—	+	—	2	C.	11.65	6.75	....	.....	.....	.....	....	9.30	— 1.4	+ 4.4	420	0.74	24	+ 3.0	+ 7.7	1,170	0.81	0.6
54 (24)	J. F.	+	—	+	—	1.5	K. H.	15.4	6.10	5.15	0	+ 2.5	1,520	4.82	9.15	+ 3.9	+11	2,490	4.49	23.15	+10.2	+10.8	5,530	3.97	4.0
55	M. P.	+	—	+	—	1.5	K. H.	17.8	6.77	3	0	+ 2.3	500	2.77	7.30	+12.1	+ 8	1,150	2.56	21	+ 6.7	+ 8	1,790	1.42	...
Diagnosis: Carcinomatosis of the Peritoneum																									
56	W. R.	—	—	—	+++	2	K. H.	.....	5.73	1	....	+ 1.5	.....	....	8.45	....	— 7.3	545	1.0.	.....	....	....	.....	....	...
Diagnosis: Normal																									
57	J. M.	—	—	—	—	2	K. H.	.....	6.22	4.30	....	+12	1,420	5.26	8.30	....	+12	2,090	4.10	.....	....	....	.....	....	...

* The changes in hemoglobin and in plasma protein are expressed in percentages of the amounts found at the time of the injection of the diuretic. + indicates a rise and — indicates a fall in amount of hemoglobin or plasma protein.
† The numbers in parentheses refer to experiments on the same patient in table 1.

The changes observed seven to thirteen hours after injection of the diuretic varied for hemoglobin from — 10.5 to + 18 per cent and for total protein from — 9.2 per cent to + 21.1 per cent.

The changes observed seventeen and one-half to twenty-eight hours after injection ranged for hemoglobin from —5.3 per cent to +22 per cent and for total protein from —9.7 per cent to +22.7 per cent.

TABLE 3.—*Correlations in Changes in Hemoglobin and/or Serum Protein After Injection of Diuretic*

	Correlation in Individual Cases Between		Coefficient of Correlation (%)*	Standard Error of This Coefficient (%)	Average of Changes in Percentage †	*Mx*	Average of Changes in Percentage †	*My*	No. of Cases *n*
	(*x*) Changes in	(*y*) Changes in	*r*						
					Patients With Edema				
A.	Hemoglobin after 7-13 hours	Protein after 7-13 hours	80.41	± 5.33	Hemoglobin after 7-13 hours	+2.60	Protein after 7-13 hours	+4.57	44
B.	Hemoglobin after 24 hours	Protein after 24 hours	65.25	± 8.67	Hemoglobin after 24 hours	+4.32	Protein after 24 hours	+3.45	44
C.	Hemoglobin after 7-13 hours	Hemoglobin after 24 hours	59.46	± 9.86	Hemoglobin after 7-13 hours	+2.23	Hemoglobin after 24 hours	+3.47	43
D.	Protein after 7-13 hours	Protein after 24 hours	73.24	± 7.15	Protein after 7-13 hours	+3.99	Protein after 24 hours	+4.35	42
					Patients Without Edema				
E.	Diuresis in 24 hours: Cc. / minute	Hemoglobin after 24 hours	59.71	±14.04	Average of diuresis in Cc. / minute	1.76	Hemoglobin after 24 hours	+7.55	21
F.	Diuresis in 24 hours: Cc. / minute	Protein after 24 hours	52.97	±14.70	Average of diuresis in Cc. / minute	1.92	Protein after 24 hours	+9.48	24

* Coefficient of correlation: $r = \dfrac{\Sigma (x \cdot y) - n \cdot M_x \cdot M_y}{\sqrt{[\Sigma (x^2) - n \cdot M_x^2]\ [\Sigma (y^2) - n \cdot M_y^2]}}$

Standard error of coefficient of correlation: $\dfrac{1 - r^2}{\sqrt{n}}$

(n : number of cases; M : average = $\dfrac{\text{Total}}{n}$)

A correlation is considered significant when the coefficient of correlation amounts to three times or more its standard error.

† The changes in hemoglobin and in plasma protein are expressed in percentages of the amounts found at the time of injection of the diuretic. + indicates a rise and — a fall in amount of hemoglobin or plasma protein.

Statistical calculations of the results of the observations are given in tables 3 and 4 and lead to the following conclusions.

1. The figures obtained by simultaneous examinations of hemoglobin and total protein seven to thirteen hours after injection of the diuretic show that the changes in hemoglobin and total protein are

highly correlated; i. e., they change in the same direction (table 3, A). The same holds true for changes in hemoglobin and total protein found after approximately twenty-four hours (table 3, B).

TABLE 4.—*Effect of Edema on Difference in Changes in Hemoglobin and Plasma Protein After Injection of Diuretic*

	Patients with Edema				Patients Without Edema				Difference of Values for Patients With Edema and Patients Without		
Changes in	No. of Patients n_x	Average of Change (%) M_x*	Standard Deviation σ_x†	Standard Error of the Average ε_x‡	No. of Patients n_y	Average of Change (%) M_y*	Standard Deviation σ_y†	Standard Error of the Average ε_y‡	Difference Between the Two Averages $M_y - M_x$	Standard Error of This Difference §	Critical Ratio ‖
G. Hemoglobin after 7-13 hours	23	−0.839	4.435	±0.925	23	+5.926	5.308	±1.107	6.765	1.442	4.691
H. Hemoglobin after 24 hours	24	−0.388	3.705	±0.776	21	+7.550	5.234	±1.142	7.938	1.381	5.749
I. Protein after 7-13 hours	27	+0.400	6.472	±1.245	24	+8.800	7.648	±1.561	8.400	1.997	4.207
J. Protein after 24 hours	24	+0.204	4.388	±0.896	24	+9.479	7.143	±1.458	9.275	1.711	5.420
K. Diuresis in 24 hours: Cc. / minute	28	1.869	0.853	±0.161	25	1.908	0.858	±0.172	0.039	0.236	0.166

* The changes in hemoglobin and in plasma protein are expressed in percentages of the amounts found at the time of the injection of the diuretic. + indicates a rise and — a fall in amount of hemoglobin or plasma protein.

† Standard deviation: $\sigma = \sqrt{\frac{\Sigma\,(x^2)}{n} - (\Sigma\,\frac{x}{n})^2}$

‡ Standard error of average: $\varepsilon = \frac{\sigma}{\sqrt{n}}$

§ Standard error of the difference between the two averages: $\sqrt{\varepsilon_x^2 + \varepsilon_y^2}$

‖ Critical ratio: $\frac{M_y - M_x}{\sqrt{\varepsilon_x^2 + \varepsilon_y^2}}$

The average of change (M) does not differ significantly from 0, if 0 is in the range of $M \pm \varepsilon$. The average of change does differ significantly from 0 if 0 does not fall in the range of $M \pm 3\varepsilon$. The difference between the two averages is significant if the critical ratio is more than 3.

2. There is a significant correlation between the changes in hemoglobin found seven to thirteen hours and approximately twenty-four hours after the injection of the diuretic in individual cases (table 3, C).

The same holds true for the changes in protein found seven to thirteen hours and twenty-four hours after injection in individual cases (table 3, D).

The results of estimations of hemoglobin and total plasma protein performed one to seven hours after the injection are not analyzed statistically, as they are small in number. It seems that the changes are in the same direction as those occurring later after the injection.

3. The results of the calculations in tables 3 and 4 also indicate that the trend of changes in hemoglobin and plasma protein is quite different in the cases in which there is edema from the trend in cases in which there is not. In the cases in which there is edema the average changes of hemoglobin and total protein observed seven to thirteen hours, as well as twenty-four hours, aften injection of the diuretic do not differ significantly from 0. On the other hand, in the cases in which there is not edema there is a significant rise in the average hemoglobin and total protein observed seven to thirteen hours, as well as twenty-four hours, after injection. The differences between the two groups of cases are statistically significant (table 4, G, H, I and J).

4. It may be expected that the changes in the hemoglobin and in the total protein will be dependent on the amount of urine and the rapidity of its production. If the renal action of mercurophylline is accepted, then the more rapid the loss of water from the blood stream, the greater the hemoconcentration, as tissue fluids may not restore the blood volume fast enough. On the other hand, assuming the primary extrarenal action of the mercurial diuretics, a rapid diuresis would lessen the tendency to hemodilution. Therefore, as the observations on the patients could not be made at exactly the same time after the injection of the diuretic, the diuresis in different patients was expressed by the quantity of urine produced per unit of time (cubic centimeters per minute). The average rate of diuresis, calculated from the quantity of urine produced in twenty-four hours, amounted in the 28 cases in which there was edema to 1.689 cc. per minute, whereas in the 25 cases in which there was not edema the average rate was 1.908 cc. per minute (table 4, K). It therefore would appear that the contrast in blood changes between the two groups, the group in which there was edema and the group in which there was not, cannot be ascribed to any difference in rate of diuresis.

5. Statistical analysis finally shows that there is a positive correlation between the rate of diuresis and the hemoconcentration in the group in which there was not edema; the higher the rate of diuresis, the higher the rise in the two blood constituents (table 3, E and F). Such a correlation could not be established for the cases in which there was edema.

The observations on the changes in hemoglobin and total plasma protein occurring after repeated administrations of mercurophylline to the same patient, in the presence or absence of edema, substantiate the principles which have been stated and will be described later.

PATIENT J. F. (clinical diagnosis: heart failure due to arteriosclerotic heart disease and hypertensive cardiovascular disease).—Experiment 24 was performed while edema was present (body weight 67.5 Kg.). The injection of mercurophylline was followed by a urinary output of 1,880 cc. in twenty-four and one-half hours, but practically no change in hemoglobin or plasma protein was discerned during this period. In experiment 54 an injection of mercurophylline was given to the same patient when edema was absent, though hepatic engorgement was still present (body weight 62 Kg.). On this occasion considerable hemoconcentration occurred. The urinary output, however, amounted to 5,530 cc. in twenty-three and one-fourth hours. This larger diuresis or the absence of edema or both may have been responsible for the hemoconcentration encountered in the second experiment.

PATIENT E. F. (clinical diagnosis: heart failure due to arteriosclerotic heart disease and hypertensive cardiovascular disease).—In the first experiment (no. 23) edema was present (body weight 53.2 Kg.). After the injection of mercurophylline a urinary output of 1,410 cc. occurred in twenty-four hours. No significant changes in the blood were observed during this period. In the second experiment (no. 53) edema was absent (body weight 50.2 Kg.). An output of 1,170 cc. in twenty-four hours occurred after injection of mercurophylline, and during the same period hemoconcentration was observed. In this case only the factor of edema can be held responsible for the difference in findings.

PATIENT B. G. (clinical diagnosis: heart failure due to rheumatic heart disease).—Mercurophylline injected while edema was present (experiment 11, body weight 49 Kg.) produced a urinary output of 2,410 cc. in twenty-three hours, associated with hemodilution. A second injection (experiment 12), given when edema was slight (body weight 45.7 Kg.), produced urinary output of 3,670 cc. in twenty-three and one half hours, and on this occasion a slight hemoconcentration was observed. After a third injection (experiment 44) in the absence of edema (body weight 43.6 Kg.) urinary output of 2,785 cc. in twenty-three and one-half hours was associated with considerable hemoconcentration. The difference in blood changes found in the first and second experiments may be partially explained by the greater diuresis which occurred in the latter. However, the quantities of urine produced during the first and the third experiment were practically the same; here only the presence or absence of edema seemed to be responsible for the difference in the changes of the blood constituents.

PATIENT F. SCH. (clinical diagnosis: heart failure due to rheumatic heart disease).—When the first experiment was performed (no. 13), edema was present (body weight 65.1 Kg.), and after the injection of mercurophylline, which was followed by excretion of 5,460 cc. of urine in twenty-three hours, hemoconcentration was observed. In the second experiment (no. 49) edema was absent, but the liver was still engorged (body weight 59.1 Kg.). On this occasion, after the injection of mercurophylline a much smaller excretion of urine was observed (2,245 cc. in twenty-four hours), but hemoconcentration of practically the same degree as in the first experiment took place. In the first experiment the diuresis was so extensive that the hemoconcentration could not be compensated sufficiently by the inter-

stitial fluid, but the inflow of edema fluid prevented a rise in the blood constituents to a level higher than that observed in the second experiment, in which the output of urine was much smaller.

PATIENT N. B. C. (clinical diagnosis: heart failure due to arteriosclerotic heart disease).—The first injection (no. 18, on Oct. 19, 1944) was given while marked edema was present; inconsistent changes were observed during diuresis

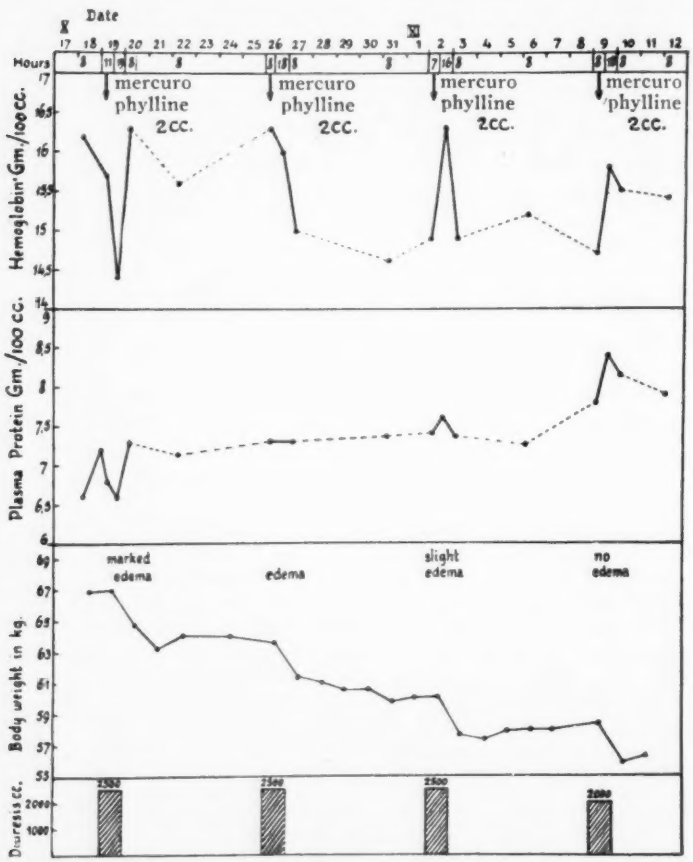

Fig. 1.—Changes in amount of hemoglobin and of plasma protein, extent of diuresis and degree of edema in patient N. B. C.

(first hemodilution, then concentration). At the time of the second injection (no. 19, on Oct. 26, 1944) edema was still present; a fall in hemoglobin was observed, but the protein level did not change. In the third experiment (no. 20, on Nov. 2, 1944) edema was slight, and a temporary rise of hemoglobin occurred. At the time of the fourth injection (no. 52, on Nov. 9, 1944) edema was absent, and a sustained rise of hemoglobin and protein was found during

diuresis. Thus with the disappearance of edema an increasing hemoconcentration took place. As the quantities of urine produced in all four experiments were practically the same, the influence of edema on the fluctuations of the amounts of hemoglobin and plasma protein is clearly demonstrated in this case.

PATIENT A. C. (clinical diagnosis: heart failure due to rheumatic heart disease).—The patient was admitted twice. During the first period of hospitalization the effect of two injections was studied (no. 50, on Aug. 15, 1943, and no. 51 on Aug. 22, 1943), edema being absent in both experiments. A sharp rise in protein occurred. A year later the patient was readmitted. Two injec-

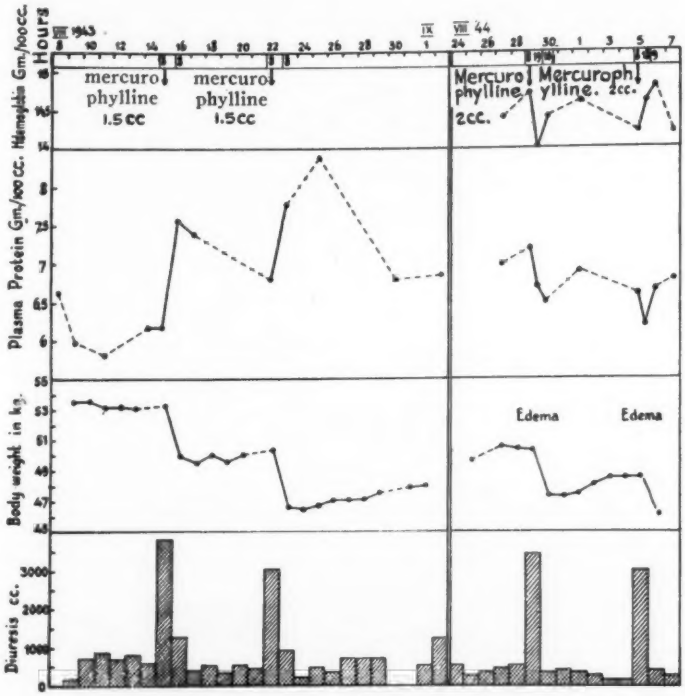

Fig. 2.—Changes in amount of hemoglobin and of plasma protein, extent of diuresis and degree of edema in patient A. C.

tions of mercurophylline were given (no. 9, on Aug. 29, 1944, and no. 10, on Sept. 5, 1944), edema being manifest on both occasions, and inconsistent small changes in the blood were observed. As the output of urine was practically the same in all four experiments, the influence of edema on the results obtained seems to be well illustrated in this case also.

PATIENT CH. W. (clinical diagnosis: heart failure due to rheumatic heart disease).—In this case three injections of mercurophylline were given (no. 40, 41 and 42), edema being absent on all three occasions. The changes in hemoglobin and plasma protein found during diuresis illustrate the influence of the

quantity of urine produced on the degree of hemoconcentration. The larger the diuresis the more pronounced the hemoconcentration.

COMMENT

Observations on fluctuations of hematocrit readings and values for hemoglobin and total plasma protein during the diuresis caused by parenteral administration of mercurial preparations have been made by various observers at different times following the injection of the drug. Differences in the time of examination of the blood may be partly responsible for the contradictory results obtained, this point having also been made by Lyons and his colleagues.[10]

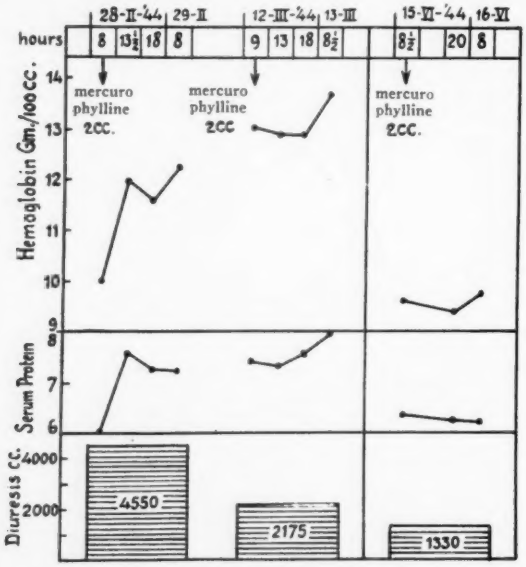

Fig. 3.—Changes in amount of hemoglobin and of serum protein and extent of diuresis in patient Ch. W.

Some investigators observed hemodilution during a short period after injection of the drug, followed by hemoconcentration later.[11]

10. Lyons, R. H.; Avery, N. L., and Jacobson, S. D.: Effect of Dehydration Produced by Mercupurin on the Plasma Volume of Normal Persons, Am. Heart J. **28**:247, 1944.

11. (*a*) Claussen, F.: Ueber die Diurese des Herzkranken, Ergebn. d. inn. Med. u. Kinderh. **43**:764, 1932; cited by Bryan and others.[20] (*b*) Meyer, P.: Untersuchungen über den kolloidosmotischen Druck des Blutes: I. Oedem und Oedemausschwemmung, Ztschr. f. klin. Med. **115**:647, 1931; (*c*) Untersuchungen

However, close analysis of the reports on this subject shows that there are inconsistencies even in results obtained over the same time intervals.

During the first four hours after injection of the diuretic a decrease in plasma protein was observed by several investigators.[12] Others noted an increase.[13] Inconsistent changes were observed by Swigert and Fitz.[14] The hematocrit value was found to be increased [15] or variable.[16] Some authors found a decrease in plasma volume.[17] Feher,[16a] on the other hand, reported an increase, and inconsistent findings were obtained by Swigert and Fitz.[14]

Numerous studies performed three to twenty-four hours after the injection of the diuretic revealed an increase in plasma protein [18] and

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über den kolloidosmotischen Druck des Blutes: II. Die Salyrgandiurese, ibid. **116**:174, 1931. (*d*) Serby, A. M.: The Pharmacology and Therapeutics of Novasurol, Arch. Int. Med. **38**:374 (Sept.) 1926. (*e*) Crawford, J. H., and McIntosh, J. F.: Use of Novasurol in Cardiac Edema, J. Clin. Investigation **1**:333, 1925; cited by Bryan and others.[20] (*f*) Kylin, E.: Studien über den kolloidosmotischen (onkotischen) Druck: Ueber die Einwirkung verschiedener Diuretika auf den kolloidosmotischen Druck, Arch. f. exper. Path. u. Pharmakol. **164**:33, 1932.

12. Bohn, H.: Experimentelle Studien über die diuretische Wirkung des Novasurols, Ztschr. f. d. ges. exper. Med. **31**:303, 1923; Fortgesetzte Studien über Novasural, seine Wirkung bei verschiedenen Lebensaltern und bei Diabetikern, sowie sein etwaiger Einfluss auf Ionenverschiebungen im Organismus, Deutsches Arch. f. klin. Med. **143**:225, 1923; cited by Lyons and others.[10] Saxl and Heilig.[1] Footnote.[11]

13. (*a*) Calvin, D. B.; Decherd, G. M., and Herrmann, G.: Plasma Protein Shifts During Diuresis, Proc. Soc. Exper. Biol. & Med. **44**:578, 1940. (*b*) Nonnenbruch, W.: Ueber die Wirkung des Novasurols auf Blut und Diurese, München med. Wchnschr. **68**:1282, 1921. (*c*) Schmitz, H. L.: Studies on the Action of Diuretics: The Effect of Salyrgan upon the Water Content of the Plasma as Measured by the Refractive Index, J. Clin. Investigation **12**:741, 1933; cited by Bryan and others.[20] (*d*) Bryan, A. H.; Evans, W. A., Jr.; Fulton, M. N., and Stead, E. A., Jr.: Diuresis Following the Administration of Salyrgan: Its Effect on Specific Gravity, the Total Nitrogen and the Colloid Osmotic Pressure of the Plasma of Normal and of Edematous Dogs, Arch. Int. Med. **55**:735 (May) 1935.

14. Swigert, V. W., and Fitz, R.: The Effect of Mersalyl (Salyrgan) on the Plasma Volume, J. A. M. A. **115**:1786 (Nov. 23) 1940.

15. Evans, W. A., Jr., and Gibson, J. G.: The Blood Volume in Diuresis, Am. J. Physiol. **118**:251, 1937.

16. (*a*) Feher, S.: Salygrandiurese und zirkulierende Blutmenge, Wien. klin. Wchnschr. **42**:964, 1929. (*b*) Swigert and Fitz.[14]

17. (*a*) Calvin, D. B.; Decherd, G. M., and Herrmann, G.: Response of Plasma Volume to Diuretics, Proc. Soc. Exper. Biol. & Med. **44**:529, 1940; (*b*) Calvin and others.[13a] Evans, and Gibson.[15]

18. (*a*) Lopes Cardozo, E.: Invloed van Salyrgan op het Bloedvolume, Nederl. tijdschr. v. geneesk. **83**:5528, 1939. (*b*) Borst, J. O. G.: Behandeling van Decompensatio Cordis door uitdrijving van keukenzout, ibid. **81**:5664, 1937. (*c*) Lyons, Avery and Jacobson.[10] Footnote 11. Footnote 13 *a*, *c* and *d*. Calvin, Decherd and Herrmann.[17a]

hematocrit value.[19] Some authors, however, found inconsistent changes in hematocrit value [20] and plasma protein [14] at this period of examination. A decrease in plasma volume was reported by some investigators,[21] while others obtained inconsistent results.[22] Thus the time factor alone does not explain satisfactorily the contradictory observations reported in the literature.

My observations on the changes in the total protein and the hemoglobin content of the blood occurring during the period of one to seven hours after injection of mercurophylline reveal that the fluctuations of these blood constituents are generally in the same direction as those occurring at later hours. The statistical analysis of my results leads to the conclusion that within a period of seven to approximately twenty-four hours after the injection the average figure obtained for changes in hemoglobin and protein is independent of the time of examination.

Differences in the type of case in which diuresis studies have been made might also be a factor responsible for the inconsistent results reported by previous observers.[10] However, there were irregular findings concerning changes in hemoglobin and plasma protein during diuresis in the same disease, for instance in heart failure,[23] in cirrhosis of the liver [11c] and in hypoproteinemia.[13d] My results also show that the underlying disease has no influence on the changes in the blood occurring during diuresis.

Analysis of my material indicates that the direction of changes in hemoglobin and plasma protein occurring during diuresis after injection of mercurophylline depends on the presence or absence of peripheral edema. In cases in which there is not edema a significant hemoconcentration generally takes place, which is the more pronounced the greater the amount of urine produced in a given time. On the other hand, in cases in which there is edema the levels of hemoglobin and total plasma protein usually remain the same.

Some observations reported previously are consistent with my observations. Lyons and his colleagues [10] consistently found hemoconcentration in normal persons during diuresis after the administration of mercurophylline. Swigert and Fitz [14] and Goldhammer and his col-

19. Lyons, Avery and Jacobson.[10] Borst.[18b]

20. (*a*) Goldhammer, S.; Leiner, G., and Scherf, D.: Ueber die zirkulierende Blutmenge vor und nach der Quecksilberdiurese, Klin. Wchnschr. **14**:1109, 1935. (*b*) Swigert and Fitz.[14] Lopez Cardoso,[18a]

21. Lyons, Avery and Jacobson.[10] Calvin, Decherd and Herrmann (footnotes 13*a* and 17*a*). Lopes Cardoso.[18a]

22. Brown, G. E., and Rowntree, L. G.: The Volume and Composition of the Blood, and the Changes Incident to Diuresis, in Cases of Edema, Arch. Int. Med. **35**:129 (Jan.) 1925. Swigert and Fitz.[14] Goldhammer, Leiner and Scherf.[20a]

23. Crawford and McIntosh.[11e] Swigert and Fitz.[14]

leagues [20a] described cases in which there was edema in which the changes in hemoglobin and total plasma protein were slight or absent. However, Evans and Gibson [15] and Bryan and his colleagues [13d] found hemoconcentration during diuresis in the presence of edema. Hemoconcentration also occurred in a few of my cases in which there was edema. It may be that other factors were predominant in the cases; nevertheless, such exceptions do not minimize the value of the general conclusions drawn from the statistical analysis of a large number of cases.

The conclusions drawn from my statistical calculations are consistent with the theory of the renal action of mercurial diuretics (though it does not explain the finding of hemodilution in a few of my cases).[24] Although the changes in hematocrit value or amounts of hemoglobin and total plasma protein cannot be considered a quantitative index of fluctuations in plasma volume,[25] it is assumed that they do indicate the direction of its change.[10]

A primary renal action of the diuretic will cause a diminution in the plasma volume with hemoconcentration. This effect will be counteracted by an inflow of interstitial fluid into the blood stream. Hemoconcentration will be slight or absent if the restoration of the plasma volume occurs quickly and adequately. This will be the case if large amounts of interstitial fluid are available. That an increase in interstitial fluid actually effects an increase in plasma volume was demonstrated by Warren and Stead.[26]

It follows that in the absence of edema hemoconcentration will take place and that it will be more pronounced when diuresis is extensive. The interstitial fluid accumulated in cases in which there is pulmonary

24. Mercupurin contains theophylline. According to Calvin and his colleagues,[17a] blood volume may be increased by the action of xanthine preparations, but as this effect passes off within six hours it has no influence on the changes observed seven to twenty-eight hours after injection.

25. Stead, E. A., Jr., and Ebert, R. V.: Relationship of the Plasma Volume and the Cell Plasma Ratio to the Total Red Cell Volume, Am. J. Physiol. **132**: 411, 1941. Ebert, R. V., and Stead, E. A., Jr.: Demonstration That the Cell Plasma Ratio of Blood Contained in Minute Vessels Is Lower Than That of Venous Blood, J. Clin. Investigation **20**:317, 1941. Kety, S. S., and Pope, A.: Cardiovascular System in Traumatic Shock, Am. Heart J. **27**:601, 1944. Beattie, J.: Fate of Transfused Plasma, Lancet **2**:445, 1942. Ebert, R. V.; Stead, E. A., Jr.; Warren, J. W., and Watts, W. E.: Plasma Protein Replacement After Hemorrhage in Dogs With and Without Shock, Am. J. Physiol. **136**:299, 1942. Hahn, P. F., and others: Red Cell and Plasma Volumes (Circulating and Total) as Determined by Radio Iron and by Dye, J. Exper. Med. **75**:221, 1942.

26. Warren, J. V.; Merrill, A. J., and Stead, E. A., Jr.: Role of Extracellular Fluid in Maintenance of Normal Plasma Volume; J. Clin. Investigation **22**:635, 1943. Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure, Arch. Int. Med. **73**:138 (Feb.) 1944.

congestion and hepatic engorgement but no peripheral edema seems unable of itself to restore the plasma volume rapidly enough after the loss of fluid through the kidney.

For a given loss of water from the blood stream the percentage change in plasma protein ought to be much larger than that in hemoglobin, as the percentage of plasma protein is related to the plasma volume while the percentage of hemoglobin is related to the total blood volume. In many instances this was actually observed (e. g., injections 47 and 48), but in others the rise in protein was the same as, or even less than, that in hemoglobin (e. g., experiments 40 and 45). In the latter case plasma protein supposedly leaves the blood stream during the period of diuresis. This possibility was pointed out by Calvin,[13a] who found that the percentage of plasma protein during diuresis with mersalyl increases less than one would expect from the decrease in plasma volume.

SUMMARY AND CONCLUSIONS

The changes in the concentration of hemoglobin and total plasma protein occurring during diuresis after the administration of mercurophylline were studied in 34 patients receiving 57 injections.

Statistical analysis showed that hemoglobin and plasma protein change in the same direction and that within a period of seven to twenty-eight hours after the injection of mercurophylline the presence or absence of hemoconcentration is independent of the time of examination. Some observations obtained one to seven hours after the injection indicate that the changes in hemoglobin and total plasma protein were essentially the same as those occurring later.

In cases in which there was edema the average changes in hemoglobin and in total plasma protein observed seven to twenty-eight hours after the injection of mercurophylline did not differ significantly from 0 in statistical analysis. In cases in which there was not edema there was a significant rise in hemoglobin and total plasma protein seven to twenty-eight hours after the injection. In the cases in which there was not edema the rise in hemoglobin and total plasma protein was higher, with an increasing rate of diuresis. In cases in which there was edema the changes in hemoglobin and total plasma protein were not dependent on the rate of diuresis.

The findings indicate that diuresis effected by mercurophylline causes a hemoconcentration which in the presence of peripheral edema is compensated by a rapid inflow of interstitial fluid into the blood stream. This interpretation is consistent with the theory of the renal action of mercurial diuretics.

Dr. M. Rachmilewitz and Prof. Dr. R. Bachi made suggestions and criticisms.

CONGENITAL DILATATION OF THE PULMONARY ARTERIAL TREE

Relation to Ayerza's Disease and Primary Pulmonary Arteriosclerosis

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AS A single lesion, unaccompanied by other developmental anomalies, congenital dilatation of the pulmonary artery appears to be an extremely rare condition. For convenience, the occurrence of this solitary congenital malformation of the pulmonary artery will be referred to throughout the remainder of this paper as "isolated congenital dilatation of the pulmonary arterial tree." Several cases have been described, but many of these were reported on the basis of clinical diagnosis without pathologic reports, and others do not meet the criteria which I consider correct for isolated congenital dilatation. These criteria are (*a*) dilatation of the entire pulmonary arterial tree with or without sclerosis; (*b*) hypoplasia of the aorta; (*c*) the absence of other congenital anomalies, such as patent ductus arteriosus or patent interauricular septum, and (*d*) the absence of other primary disease of the heart or lungs and of primary arterial disease such as rheumatism or syphilis. When these criteria are applied to the cases reported in the literature under the name "congenital dilatation of the pulmonary artery," only 4 cases meet the requirements.

Perusal of the literature on other conditions in which dilatation of the pulmonary artery is supposed to be a feature led to the conclusion that some of the cases reported as Ayerza's disease and some of those listed as primary pulmonary sclerosis might well be fitted into the group of cases of isolated congenital dilatation. Nevertheless, the total still would not exceed 10 or 12 cases.

The first mention of congenital pulmonary dilatation was made by Zuber [1] in 1904. He described a case which does not belong to the restricted group under discussion because it showed patency of the ductus arteriosus. Assman's [2] cases also presented other congenital lesions, but his name is mentioned because he was the first to postulate unequal

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1. Zuber, B.: Ueber einen noch nie beschriebenen Fall von hochgradiger, angeborener Erweiterung der Arteria pulmonalis in toto, Jahrb. f. Kinderh. **59**: 30-53, 1904.

2. Assman, H.: Röntgendiagnostik der inneren Krankheiten, ed. 4, Leipzig, F. C. W. Vogel, 1929.

division of the truncus arteriosus communis as a possible origin for this condition.

In 1933 Oppenheimer [3] reported 8 cases under the title "Idiopathic Dilatation of the Pulmonary Artery." Although only 2 of these were confirmed at autopsy, both showed an enlarged pulmonary arterial tree, a small aorta and hypertrophy of the right ventricle, the pulmonary artery in each case showing "arteriosclerosis without compromising the lumen."

The cases of Smith and others,[4] Johnson [5] and Heimann and Posel [6] showed other associated lesions, or were reported without confirmation at autopsy.

"Enormous" enlargement of the pulmonary artery with a small aorta was reported by Routier and Brumlik,[7] but the coexistence of chronic pulmonary disease lays these cases open to question, even though the presence of a small aorta supports the likelihood that there was a congenital basis for the dilatation. It is interesting to note that these authors argued against the commonly held view that disease of the lungs gives rise to dilatation of the pulmonary arterial tree; they contended that the congenital anomaly predisposes to chronic affections of the lung. The French workers generally accept the concept of unequal division of the truncus arteriosus communis as the source of atrial septal defect and of pulmonary dilatation, but, since most of their writings deal with the former, their cases are not included. Thus, only one of the cases of both Laubry and others [8] and Kourilsky and others [9] falls into the group of isolated congenital dilatation of the pulmonary artery.

Brenner's [10] excellent work on the pathology of the pulmonary vessels contains an analysis of 20 cases of Ayerza's disease, some of which

3. Oppenheimer, B. S.: Idiopathic Dilatation of the Pulmonary Artery, Tr. A. Am. Physicians **48**:290-297, 1933.

4. Smith, L. A.; Moenning, W. P., and Bond, G. S.: Dilatation of the Pulmonary Artery of Congenital Origin, Radiology **27**:141-148 (Aug.) 1936.

5. Johnson, S. E.: Congenital Dilatation of the Pulmonary Arteries Revealed by Roentgenkymography, Ann. Int. Med. **10**:546-549 (Oct.) 1936.

6. Heimann, H. L., and Posel, M. M.: A Case of Congenital Dilatation of the Pulmonary Artery, Brit. M. J. **2**:512 (Oct. 23) 1943.

7. Routier, D., and Brumlik, J.: Dilatation congénitale de l'artère pulmonaire, Arch. d. mal. du cœur. **33**:184-186 (March-April) 1940.

8. Laubry, C.; Routier, D., and Heim de Balsac, R.: Grosse pulmonaire: Petite aorte, affection congenitale, Bull. et mém. Soc. méd. d. hôp. de Paris **56**: 847-850 (Jan. 16) 1941.

9. Kourilsky, R.; Guede, M., and Regaud, J.: Les dilatations congénitales de l'artère pulmonaire, Bull. et mém. Soc. méd. d. hôp. de Paris **56**:772-779 (Jan. 6) 1941.

10. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. **56**:211-237 (Aug.); 457-497 (Sept.); 724-752 (Oct.); 976-1014 (Nov.); 1189-1241 (Dec.) 1935.

showed a large pulmonary artery and a small aorta. He also clearly defined primary pulmonary sclerosis as being sclerosis accompanied by hypertrophy of the right side of the heart, but without other pulmonary or cardiac disease. Of all the reported cases, only 16 were found to fit his definition, and of these, 6 showed moderate pulmonary dilatation. Norris [11] reported a case with a large pulmonary artery. DeNavasquez and others [12] published reports of 3 cases in which large sclerotic pulmonary arteries were found, along with a hypertrophic right ventricle in each instance. East [13] also reported 3 cases of primary pulmonary arteriosclerosis in which large pulmonary arteries were found. It is possible that these 7 cases may have had a congenital origin, although I cannot be as certain of this as are some other authors.

It is thus evident that the literature contains only a very small number of cases that can be definitely identified as isolated congenital dilatation of the pulmonary arterial tree, together with a few others which may or may not be included. Herewith is presented an instance of dilatation of the pulmonary artery accompanied by definite sclerotic change in the pulmonary arterial tree, and without demonstrable lung disease, syphilis, rheumatism, or failure of the left side of the heart. It might, then, have been offered as an example of primary pulmonary arteriosclerosis or as a case of Ayerza's disease, but an attempt will be made to show that it rightfully belongs to the group of cases of isolated congenital dilatation.

REPORT OF A CASE

Clinical Summary.—The patient, a 41 year old white woman, was admitted to the medical service of the Royal Victoria Hospital on June 21, 1944, complaining of dyspnea and palpitations, which she stated had been present for seven years. She stated, too, that at the age of 7 she had been found to have a heart murmur on physical examination. She had not had rheumatic fever. In 1935 a uterine suspension and an appendectomy had been performed. Since 1937 there had been two attacks of circulatory failure. In 1940 the patient first noticed cyanosis of the finger tips. She was admitted to the hospital at that time, and investigation revealed a palpable thrill, systolic in time, and felt all over the precordial region. The heart was enlarged to the right, and there was a systolic murmur at the left sternal border. The blood pressure was 125 systolic and 85 diastolic. Reaction to the Wassermann test was negative. The electrocardiogram showed right axis deviation. Fluoroscopic examination showed a dilated pulmonary conus, pulsa-

11. Norris, R. F.: Primary Pulmonary Arteriosclerosis: Report of Case with Marked Calcification of Pulmonary Arteries, Bull. Johns Hopkins Hosp. **59**:143-153 (Sept.) 1936.

12. DeNavasquez, S.; Forbes, J. R., and Holling, H. E.: Right Ventricular Hypertrophy of Unknown Origin: So-Called Pulmonary Hypertension, Brit. Heart J. **2**:177-188 (July) 1940.

13. East, T.: Pulmonary Hypertension, Brit. Heart J. **2**:189-200 (July) 1940.

tion of the pulmonary vessels and hypertrophy of the right ventricle. The clinical diagnosis was patent ductus arteriosus. The patient was discharged on a regimen of rest. Her course was uneventful until three weeks before the final admission, in June of 1944, when she began to have fever (temperature elevated to 103 F.) and chills. She was put to bed at home, awaiting accommodation in the hospital.

On June 21, the day of admission, the temperature was 102 F., pulse rate 88, respirations 22 and blood pressure 124 systolic and 78 diastolic. The heart presented the same picture as before, and there was cyanosis of the finger tips and toes.

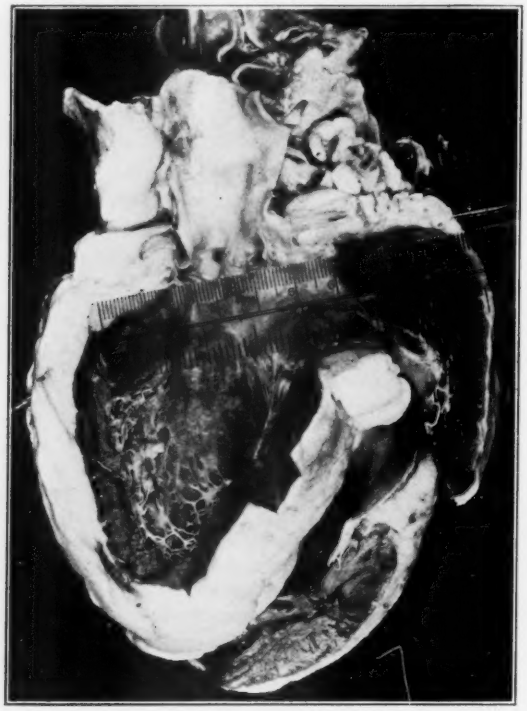

Fig. 1.—Photograph of heart showing the left ventricle and the small aorta. Note also the great hypertrophy of the right ventricle, the cut edge of which is seen at the lower right.

The liver was just palpable. The leukocyte count was 12,400, and the red cell count was 5,200,000. A blood culture on the day of admission yielded 22 colonies of Streptococcus viridans per cubic centimeter. The clinical impression was that the patient suffered from bacterial endarteritis in a patent ductus arteriosus.

Sulfonamide therapy was instituted, and the temperature dropped, but soon rose again. The patient was transferred to the department of surgery, where an operation was performed to tie off the ductus arteriosus. The patient's condition deteriorated rapidly, however, and she died in the operating room.

Postmortem Examination.—A complete autopsy was performed three hours after death. In the following summary only the pertinent findings are given in detail.

The heart showed tremendous hypertrophy of the right side (weight, 555 Gm.) and slight dilatation. The valves were essentially normal. The aortic valve ring was small, having a circumference of only 4 cm., and the entire aorta was remarkably small, its circumference averaging about 3.5 cm. (fig. 1). The pulmonary valve ring was large, measuring 7.5 cm. in circumference. The pulmonary artery was definitely larger than normal (8 cm. in circumferance, fig. 2), and the

Fig. 2.—Photograph of heart showing the hypertrophied right ventricle and the dilated pulmonary artery.

branches were considerably enlarged out to the periphery of the collapsed lungs. The entire pulmonary arterial tree showed distinct arteriosclerosis, and on section of the lungs, the smaller branches stood out prominently because of their size and thickness (fig. 3). In addition, some of the larger branches were filled with adherent thrombi. The aorta showed only minimal arteriosclerosis. The ductus arteriosus was easily identified, and around it were two heavy silk ligatures. The aortic orifice of the ductus arteriosus was represented only by a "dimple" about which there was some arteriosclerotic change. It admitted the tip of a

probe. There was a smaller "dimple" on the pulmonic side, but there was no communication between the two. There were no vegetations found in relation either to the obliterated ductus or to any of the heart valves. The lungs presented a striking degree of collapse but exhibited no gross evidence of fibrosis or emphysema (fig. 3).

Fig. 3.—Photograph of the posterior halves of both lungs. Dilatation and sclerosis of all the branches of the pulmonary arterial tree can be seen. Some of these vessels are plugged with thrombus material. The lungs are atelectatic.

Microscopic Examination.—The pulmonary aorta and its large and medium-sized branches within the lungs differed strikingly from the normal in the great width of their lumens. It was especially noteworthy that the medial coat of the pulmonary aorta was not thicker than that of the normal pulmonary trunk, and indeed appeared, if anything, somewhat thinner, even in areas where no arteriosclerotic thickening of the intima complicated the picture. So too, in the large

and medium-sized branches of the pulmonary artery the medial coat was conspicuously thin in relation to the large diameter of their lumina (fig. 4). All of these vessels presented numerous areas of arteriosclerotic thickening of the intima, and the largest exhibited the formation of atheromatous cavities in their depths. Beneath such lesions the media was even thinner than elsewhere. In several of the large and medium-sized branches of the pulmonary artery thrombi of varying ages occupied the lumen, seldom, however, obstructing it completely. Most of these thrombi were partly or almost completely organized, but some of them, lying in relation to severe arteriosclerotic intimal lesions, presented hyaline fusion and loss of cellular structure such as to suggest old thrombus material that had not become organized. The surfaces of such thrombi in a few places showed addi-

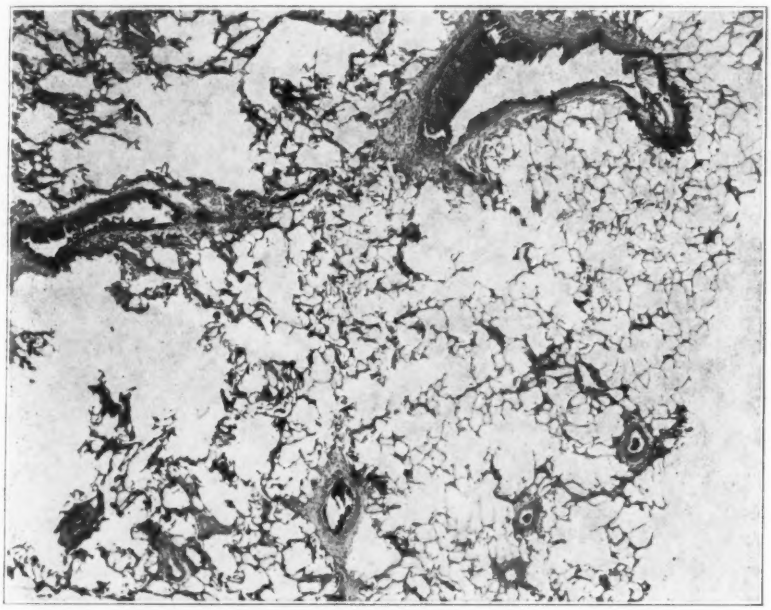

Fig. 4.—Photomicrograph of lung near periphery. Dilatation and sclerosis of small arterial branches are evident (× 15).

tional deposits of fresh thrombus material. The small arteries and arterioles throughout the parenchyma of the lung did not present such an obvious disproportion between the thickness of the media and the size of the lumen even in those vessels that were free from arteriosclerotic thickening of the intima (fig. 4). Such vessels, however, were relatively few in comparison with the large numbers of arteries of this size that were considerably affected by concentric fibrous thickening of the intima. The latter varied in degree from minimal subintimal increase of collagen to a dense fibrous thickening of the intima that reduced the lumen to an extreme degree (fig. 5). Other small arteries were honeycombed with multiple channels lined with endothelium and separated from one another by more or less cellular fibrous connective tissue (fig. 6). This appeared to be the result

of organization and recanalization of thrombus material. The obliterated ductus arteriosus was cut in serial sections, examination of which revealed no trace of a persistent lumen anywhere. The parenchyma of the lungs presented a widespread though moderate degree of atelectasis. In some patches the collapse was complete, giving an appearance of density suggestive of possible fibrosis, but special stains for fibrous connective tissue revealed no significant increase of collagen in these areas or elsewhere in the lung. There was no evidence of emphysema apart from the rupture of a few of the alveolar walls in widely scattered areas. The alveolar spaces were everywhere free from exudate. The liver presented histologically rather slight evidence of chronic passive hyperemia.

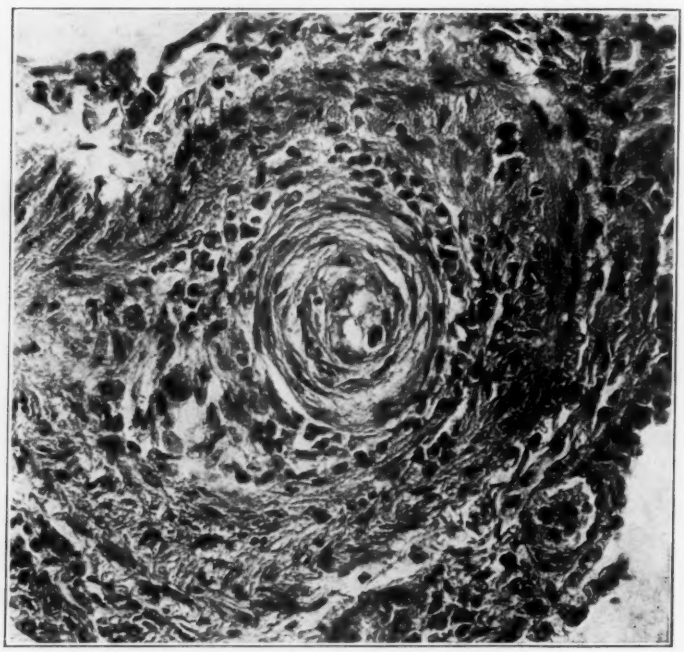

Fig. 5.—Photomicrograph of small artery of lung. Note concentric laminated proliferation of the intimal layer and extreme narrowing of the lumen (× 360).

Bacteriologic Examination.—Postmortem cultures of the heart's blood yielded no growth aerobically or anaerobically.

COMMENTS

It is generally agreed that dilatation of the pulmonary artery is a feature of Ayerza's disease and that dilatation is frequently associated with primary sclerosis of the pulmonary artery. Therefore it is evident, from the foregoing description, that this case might be considered to represent any one of three conditions, namely Ayerza's disease, primary

pulmonary arteriosclerosis or isolated congenital dilatation of the pulmonary arterial tree.

Opinion as to the definition of Ayerza's disease is still extremely varied and confusing. Some authors group all cases of cyanosis, dyspnea and erythrocytosis of pulmonary origin under this term. Some say that the clinical manifestations are correlated with sclerosis of pulmonary vessels due to syphilis. Others believe Ayerza's disease to be due to sclerosis secondary to changes in pulmonary tissue and have written extensively of chronic bronchopulmonary disease as the under-

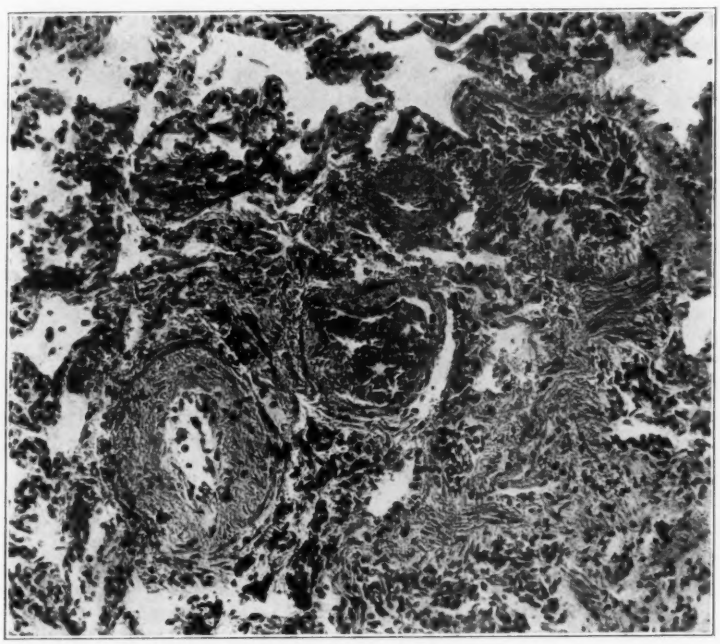

Fig. 6.—Photomicrograph of lung with small arteries showing distinct intimal proliferation. One vessel (at center) presents multiple channels probably produced by recanalization of thrombus (× 160).

lying cause. Brenner [10] collected from the literature 20 cases described under the title of Ayerza's disease. Among these there was, in general, enlargement of the right side of the heart and, to a lesser extent, of the left side of the heart. In some cases there was coronary sclerosis, and in some, mitral stenosis. Besides pulmonary arteriosclerosis there was bronchitis, bronchiectasis, emphysema or pulmonary fibrosis in almost all of the cases. As mentioned previously, some of these cases exhibited a small hypoplastic aorta. Thus, some of the cases reported as Ayerza's

disease are merely examples of secondary sclerosis of the pulmonary artery; others, and these are very few, are cases of primary pulmonary sclerosis, and some very probably are cases of congenital dilatation of the pulmonary arterial tree. Brenner said of Ayerza's disease, "It is clear that there is nothing specific about the symptoms which are ordinarily recognized as being those of heart failure secondary to chronic lung disease . . . there is almost always pulmonary sclerosis which is less marked than in some cases which show no heart symptoms. There is no good reason for retaining the term Ayerza's disease." This is a conclusion in which I heartily concur.

As regards primary pulmonary arteriosclerosis, Brenner concluded that it is not a pathologic entity, but several conditions included under the same name. Although several theories exist as to the cause of the condition, none is universally applicable, and Brenner felt that there must be many causes that could produce the same final morbid picture.

The relation between pulmonary sclerosis, pulmonary hypertension and pulmonary dilatation might well be discussed here. It is probable that raised tension in a pulmonary vessel can give rise to sclerosis, even though this is difficult to prove experimentally. For instance, Karsner, Simon and Fujiwara[14] could not show that hypertension in the pulmonary circuit of experimental animals caused sclerosis of the pulmonary vessels. That sclerosis of the main branches of the pulmonary artery can cause a raised tension is more difficult to believe. Yet it is felt by many that dilatation of the pulmonary arteries can be caused by increased intravascular tension due to pulmonary arteriosclerosis. In mitral stenosis there are often found sclerotic changes in the pulmonary arteries and arterioles of a most severe degree, and yet there is no general dilatation of the pulmonary tree. The example of mitral stenosis can be used also to throw doubt on the belief that raised tension can cause dilatation, because here, besides the presence of sclerosis, there is back pressure in the pulmonary circuit with ensuing pulmonary hypertension. Simon[15] states that in none of his experimental animals in which hypertension was definitely produced in the pulmonary circuit was any dilatation found. It would appear, therefore, that sclerosis and/or raised pulmonary tension is not enough to cause dilatation. It follows from this that in the cases of so-called primary pulmonary arteriosclerosis which do show a high degree of dilatation there must be some additional factor to account for the dilatation.

There appears to be good reason for believing that the dilatation of the pulmonary arteries in such cases is dependent on a congenital dispro-

14. Karsner, H. T.; Simon, M. A., and Fujiwara, T. F.: The Relation of Experimental Pulmonary Arterial Hypertension to Arteriosclerosis, Arch. Path. **31**:585-591 (May) 1941.

15. Simon, M. A.: Personal communication to the author.

portion in the size of the pulmonary arterial tree relative to the rest of the vascular system. The outstanding argument for the concept of a congenital origin is the association of a hypoplastic aorta. Cases that show this combination, I am convinced, are definitely congenital in origin. Those instances of dilatation of the pulmonary tree not associated with hypoplasia of the aorta may also be of congenital origin, but the evidence is not so strong in such cases. It seems certain that the large pulmonary artery and small aorta seen in the case reported here are based on an unequal division of the truncus arteriosus communis. The apparent great rarity of this combination as an isolated condition is explained by the fact that it is much more frequently associated with a congenital defect in the interauricular septum, to which the main attention is often directed to the exclusion of interest in the large pulmonary artery. In seeking an explanation for the large size of the pulmonary artery in so many cases of atrial septal defect, Taussig, Harvey and Follis [16] said, "the cause . . . is obscure . . . it appears to be *ipso facto* a congenital malformation which frequently accompanies a defect in the interauricular septum." Again, Laubry and others [8] and Kourilsky and others [9] emphasized the importance of unequal division of the truncus arteriosus communis in the development of atrial septal defect. Evidently this unequal division can lead to septal defect, together with congenital dilatation of the pulmonary vessels, or to "isolated" congenital dilatation of the pulmonary arterial tree.

Given a large pulmonary artery and a small aorta as a congenital malformation, how does the former become sclerotic? It is well known that when there is a column of fluid at constant pressure in a cylinder, the stress or stretching force at any point in the wall of the cylinder is directly proportional to the diameter of the column. Therefore, with the same internal pressure, the stress or stretching force on the wall of a large vessel is greater than that on a small one, and the stress on a dilated vessel wall is greater than it would be were the diameter of the vessel normal. To withstand successfully the increased stress, the wall of the dilated vessel would have to be thicker in proportion to the increase of its diameter, and there is no evidence to indicate that in the present case the dilated pulmonary arteries were thicker than normal before the arteriosclerosis developed. If one accepts the hypothesis that arteriosclerosis is a degenerative lesion which may be initiated by the mechanical effects of an increased stress on the vessel wall,[17] then the development

16. Taussig, H. B.; Harvey, A. M., and Follis, R. H., Jr.: The Clinical and Pathological Findings in Interauricular Septal Defect: Report of Four Cases, Bull. Johns Hopkins Hosp. **63**:61-89 (Aug.) 1938.

17. Moschcowitz, E.: Vascular Sclerosis, London, Oxford University Press, 1942.

of arteriosclerosis in the congenitally dilated pulmonary tree is adequately explained. Abnormal stretching forces in the wall of a vessel may originate from increased diameter of the vessel alone without the necessity of increased hydrostatic pressure, and that is the crux of the argument.

Accordingly, the case presented here is interpreted as having included initially only a congenital malformation in the form of dilatation of the pulmonary arterial tree without proportionate increase in the thickness of the media of the dilated vessels. This condition exposed the unduly thin walls to abnormal stretching forces, which initiated arteriosclerotic changes in the absence of pulmonary hypertension. Eventually, obstruction of some of the large and medium-sized pulmonary arteries by thrombus material and of small arteries by encroachment of arteriosclerotic intimal thickening on their lumens led to increased pulmonary pressure, right-sided cardiac hypertrophy, and final cardiac failure under the stress of a major surgical procedure.

The existence of primary pulmonary arteriosclerosis cannot be questioned, and those cases which show slight dilatation of the pulmonary arteries, sclerosis of no apparent cause and right-sided cardiac hypertrophy must be classed together, and their cause and pathogenesis left a question. However, some of the cases reported under this heading, in which the pulmonary vessels are dilated, including Brenner's case 2, probably have a congenital origin. Pulmonary arteriosclerosis can exist to a considerable degree without hypertrophy of the right side of the heart and is therefore, by Brenner's definition, not primary pulmonary arteriosclerosis. This fact suggests that the hypertrophy in primary pulmonary arteriosclerosis may be as primary as the sclerosis itself, both having a common unknown cause (Brenner [10]). As regards isolated congenital dilatation, the French workers are of the opinion that the hypertrophy of the right side of the heart in these cases also has a congenital basis, the same developmental imbalance giving rise to the dilated pulmonary artery, the small aorta and the disproportionate size of the right side of the heart. Congenital dilatation of the pulmonary artery might be classified as a subgroup of primary pulmonary sclerosis, and this is in agreement with Brenner's idea that primary sclerosis is several conditions included under one name.

As regards the clinical picture, Bedford, Papp and Parkinson [18] grouped primary pulmonary arteriosclerosis with congenital pulmonary dilatation under the term "primary dilatation." They stated that in advanced stages the clinical picture is identical with that of atrial septal defect and that differential diagnosis may be impossible during life. As

18. Bedford, D. E.; Papp, C., and Parkinson, J.: Atrial Septal Defect, Brit. Heart J. **3**:37-68 (Jan.) 1941.

has been seen from the present case, the two conditions may also be easily confused with patency of the ductus arteriosus. In 1943 Grishman, Steinberg and Oppenheimer [19] reported their work on angiocardiography and said that by this means they could make the diagnosis during life with a fair degree of certainty. Accurate clinical diagnosis, of course, is important, in view of the growing feasibility of the operative treatment for patency of the ductus arteriosus.

SUMMARY AND CONCLUSIONS

1. The name "isolated congenital dilatation of the pulmonary arterial tree" is suggested as a term to indicate the occurrence of this condition in the absence of other congenital malformations in the circulatory system with the single exception of a hypoplasia of the aorta, which is a frequent corollary to the largeness of the pulmonary arterial system.

2. The great rarity of this condition is demonstrated by a review of the literature.

3. A case that presented a dilated arteriosclerotic pulmonary tree and a hypoplastic aorta is reported.

4. Discussion of Ayerza's disease and of primary pulmonary arteriosclerosis in relation to isolated congenital dilatation of the pulmonary arterial tree leads to the conclusion that the case presented is an example of the latter condition.

5. A theory to explain the development of arteriosclerosis in the congenitally dilated pulmonary tree is suggested.

6. The clinical features of the condition under consideration are briefly indicated.

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19. Grishman, A.; Steinberg, M. F., and Oppenheimer, B. S.: The Clinical Diagnosis of Idiopathic Dilatation of the Pulmonary Artery, J. Mt. Sinai Hosp. **10**:142-149 (May-June) 1943.

Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1944 to June 1945

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AND
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INTRODUCTION

THE NUMBER of articles published from July 1944 to June 1945 is surprisingly large when one recalls that this period represents the peak of the war effort. There was a significant increase in the attention given military gastroenterology, but civilian gastroenterology continued to receive nevertheless the main emphasis.

Developments in the physiology of the digestive tract during 1943 and 1944 have been reviewed by Babkin and Friedman [1]; Breitwieser and Miller [2] have discussed recent advances in the entire field of gastroenterology. Clark [3] in a good discussion of abdominal pain emphasizes the frequency with which diaphragmatic hernia, disease of the gallbladder and functional derangements of the digestive tract may mimic or accentuate cardiac disease or its symptoms; Scott [4] brings out the reverse condition.

Brennemann's [5] review of abdominal pain in children is a classic to be read with profit by every one interested in the subject. His final comment is of particular interest: "In conclusion I can only say that the majority of abdominal pains encountered in private practice, which gives a truer picture of actual incidence than is found in hospital practice,

From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

1. Babkin, B. P., and Friedman, M. H. F.: Digestive System, in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1945, vol. 7, pp. 305-330.

2. Breitwieser, E. R., and Miller, T. G.: Recent Advances in Gastro-Enterology, M. Clin. North America **28**:1349-1361, 1944.

3. Clark, W. E.: Gastrointestinal Conditions Simulating or Aggravating Cardiovascular Disease, J. A. M. A. **128**:352-355 (June 2) 1945.

4. Scott, J. W.: Gastrointestinal Symptoms in Cardiovascular Disease, Canad. M. A. J. **52**:128-130, 1945.

5. Brennemann, J.: Abdominal Pain in Children, J. A. M. A. **127**:691-695 (March 24) 1945.

have in my experience, been of unknown nature and unknown etiology." Campbell [6] calls attention to the frequency with which urologic disease may cause abdominal pain in children. Strauss [7] in a discussion of the differential diagnosis of abdominal pain in children stresses the difficulty caused by the confusing of the exanthems with mesenteric lymphadenitis or with appendicitis, by the presence of gastrointestinal anomalies and by the fatty condition of the abdomen so often encountered in young children, which hinders proper abdominal palpation and percussion. Allen [8] gives an excellent review of the present status of abdominal surgery.

Aaron [9] summarizes the various drugs used in the treatment of gastrointestinal conditions and the best methods of administration and reviews the treatment of inflammatory lesions of the upper part of the gastrointestinal tract. Gray [10] discusses the role in gastrointestinal disease of occupational hazards, including metal intoxications, such as lead, arsenic and mercury poisoning and solvents, such as carbon tetrachloride, benzene, the chlorinated naphthalenes and diphenyls; McGee, McCausland, Preston and Houff [11] describe the disturbances resulting from trinitrotoluene intoxication.

Gibb [12] reviews his gastroenterologic experience in a large rear area naval hospital and concludes that it approximated that of civilian life.

ANOREXIA NERVOSA AND FUNCTIONAL DISORDERS

Berkman [13] notes again that patients with anorexia nervosa are not concerned by their loss of weight or their cachectic appearance and evade a discussion of the emotional factors precipitating the anorexia or the vomiting. Amenorrhea occurred in 50 per cent of his cases, but there were no recognizable avitaminoses. In women over 30, the

6. Campbell, M. F.: Abdominal Pain Due to Urologic Disease in Children, J. A. M. A. **128**:326-329 (June 2) 1945.

7. Strauss, A. A.: Abdominal Pain in Children from a Surgical Standpoint, J. A. M. A. **128**:330-335 (June 2) 1945.

8. Allen, A. W.: Medical Progress in Abdominal Surgery, New England J. Med. **232**:165-173, 1945.

9. Aaron, A. H.: Comment on Drugs Frequently Used in the Treatment of Gastrointestinal Conditions, Clinics **3**:663-671, 1944; Inflammatory Lesions of the Upper Gastrointestinal Tract, J. A. M. A. **127**:1027-1030 (April 21) 1945.

10. Gray, I.: Gastrointestinal Disease in Relation to Occupational Hazards, Gastroenterology **4**:61-71, 1945.

11. McGee, L. C.; McCausland, A.; Preston, J. F., Jr., and Houff, L. A.: Metabolic Disturbances in Workers Exposed to Trinitrotoluene, Gastroenterology **4**:72-82, 1945.

12. Gibb, W. T.: Gastroenterology in a Large Naval Hospital, South. M. J. **37**:507-510, 1944.

13. Berkman, J. M.: Anorexia Nervosa: The Diagnosis and Treatment of Inanition Resulting from Functional Disorders, Ann. Int. Med. **22**:679-691, 1945.

incidence of the disease is low, but the therapy is more difficult. Treatment consists in discussion of the emotional factors and consumption of a high protein diet adjusted to the caloric needs of the patient, in which the number of calories is increased by 300 every five to six days. The mechanism and the significance of the amenorrhea should be discussed with the patients.

Rush [14] discusses the recognition and the treatment of anxiety neuroses presenting predominantly gastrointestinal symptoms in an overseas army hospital and describes some instructive cases. "The early recognition and treatment of these patients is the most important factor in preventing the establishment of a permanent neurosis." Carleton's [15] experience in the Navy was similar.

Alvarez [16] emphasizes how little is known even today about the nature, the origin, the mode of production and the significance of the common symptoms physicians are constantly called on to relieve. Heartburn consists of a burning (sometimes painful) or rending distress located usually under the lower end of the sternum and running up as far as the pharynx. Few of the 123 patients with heartburn had any organic disease of the digestive tract. In 17 patients who had or had had ulcer it was noted that when the ulcer was active and hunger pain was present heartburn was absent. Conversely, when heartburn was present, the ulcer seemed to be healed. Heartburn usually comes in "spells" lasting from days to weeks, months or years. The degree of acidity of the gastric content is not important.

Alvarez [17] also describes 2 cases of a rare syndrome resembling the gastric crisis of tabes and related to that seen in "nervous bloaters." One of the patients, a woman, suffered for years from frequent and very painful "spells" which came suddenly, lasted a few hours and disappeared suddenly. During the "spell" the abdominal wall was flat and boardlike; severe, labor-like pains came and went every four minutes or so. There was nothing else to suggest any disturbance of function of the digestive tract. Morphine in doses of 1 or 2 grains (0.065 or 0.13 Gm.) had little effect on the pain but somewhat shortened the spells. Exploratory operations and a necropsy failed to reveal any cause for the disease. The second patient, also a woman, who appeared to have hysterical tendencies and lived a stormy life with a dipsomaniac, suffered for years from spells resembling those of the

14. Rush, A.: The Anxiety Neuroses Manifested by Gastrointestinal Symptoms, M. Clin. North America **28**:1541-1543, 1944.

15. Carleton, W. T.: Gastrointestinal Tract Disturbances: Functional Disturbances on a Psychogenic Basis, U. S. Nav. M. Bull. **44**:538-548, 1945.

16. Alvarez, W. C.: Heartburn, Gastroenterology **3**:1-12, 1944.

17. Alvarez, W. C.: A Rare Syndrome of Crisislike Abdominal Pain, Gastroenterology **4**:296-304, 1945.

first woman, with the difference that she bloated distressingly and sometimes retched. On one occasion an attack began with spasm only of the muscles in the left upper quadrant of the abdomen. At times when the woman's attention was distracted by vomiting, the abdominal muscles relaxed and the bloating disappeared, only to reappear instantly when her abdomen was touched and her attention drawn to it. The clinical picture appeared to represent a link between that presented by the first type of patient and that of the "nervous bloaters" who have no gas in the bowel. The diagnosis of hysteria seems acceptable in the second case, less so in the first one.

Brooke [18] reports 4 cases of massive gastrointestinal hemorrhage occurring one to four days after a minor surgical operation and considered to be nervous in origin. However, in 1 patient the roentgenographic findings were considered compatible with duodenal ulcer; negative findings were reported in 2; the fourth had no roentgenologic examination. Gastroscopic studies were not made. [The reviewers are unable to accept these as bona fide instances of hemorrhage on a "psychic or emotional basis."]

ESOPHAGUS

Review.—Benedict [19] analyzes 30 papers dealing with diseases of the esophagus and published during the years 1942 and 1943.

Roentgenologic Appearance.—In a beautifully illustrated article, Calthrop [20] demonstrates the great value of the examination. Bakwin, Galenson and LeVine [21] show that in infants the esophagus is a distensible tube as wide or wider than the vertebral column.

Anomalies.—Ladd and Scott [22] in an excellent paper present the anomalies and the problems encountered in the treatment of 5 patients. Esophageal duplications of developmental origin may form mediastinal cysts along the course of the esophagus. These cysts have muscular walls and mucous membrane linings simulating gastric mucosa and subject to peptic ulceration. Surgical extirpation is best accomplished by

18. Brooke, P. A.: Gastrointestinal Bleeding on a Psychic or Emotional Basis Following Minor Surgical Procedures, Clinics **3**:997-1002, 1944.

19. Benedict, E. B.: Esophagus: Review of Literature 1942 and 1943, Gastroenterology **3**:90-97, 1944.

20. Calthrop, G. T.: Radiology in Diseases of the Oesophagus, Post-Grad. M. J. **20**:282-286, 1944.

21. Bakwin, H.; Galenson, E., and LeVine, B. E.: Roentgenographic Appearance of the Esophagus in Normal Infants, Am. J. Dis. Child. **68**:243-247 (Oct.) 1944.

22. Ladd, W. E., and Scott, H. W., Jr.: Esophageal Duplications or Mediastinal Cysts of Enteric Origin, Surgery **16**:815-835, 1944.

marsupialization and subsequent destruction of the mucosal lining. Three of the 5 patients recovered.

Haight [23] analyzes the findings in 32 patients with congenital atresia. In all the upper segment ended as a blind pouch. Twenty-six had a communication between the lower esophageal segment and the trachea or a bronchus. A primary anastomosis of the upper and lower esophageal segments was done in 16 of the 24 patients for whom an exploration of the anomaly was undertaken. Six, or 37.5 per cent, of the 16 patients are living, seven months to three years after operation—the best results obtained thus far with this operation. The reconstructed esophagus is patent in all instances.

Daniel Jr.[24] reports 7 cases of congenital atresia. An end to end anastomosis was successfully performed in 1. Four additional cases are reported, with survival of seven months in 1.[25]

Fistula.—Moersch and Tinney [26] report 39 cases of acquired fistula between the esophagus and the tracheobronchial tree: In 36 per cent it was due to carcinoma of the esophagus; in 13 per cent, to trauma; in 10 per cent, to syphilis; in 10 per cent, to tuberculosis, and in 5 per cent, to diverticulosis of the esophagus. Death is usually the result of aspiration pneumonia or of mediastinal or pulmonary abscesses. Surgical measures may be of value, particularly in those instances in which the fistula is a result of trauma.

Aneurysm.—A syphilitic aneurysm of the aorta that ruptured into the esophagus is reported.[27]

Rupture.—Another instance of spontaneous rupture of the esophagus occurring after a heavy meal is described, apparently the third case to be diagnosed before death![28] A longitudinal tear three fourths of an inch long (about 2 cm.), beginning an inch above the diaphragm, was repaired surgically, but the patient died within twenty-four hours.

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23. Haight, C.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula: Reconstruction of Esophageal Continuity by Primary Anastomosis, Tr. Am. Surg. A. **62**:623-655, 1944; Ann. Surg. **120**:623-655, 1944.

24. Daniel, R. A., Jr.: Congenital Atresia of the Esophagus, with Tracheo-Esophageal Fistula, Ann. Surg. **120**:764-771, 1944.

25. Singleton, A. O., and Knight, M. D.: Congenital Atresia of the Esophagus, with Tracheo-Esophageal Fistulae: Transpleural Operative Approach, Tr. South. S. A. (1943) **55**:267-283, 1944.

26. Moersch, H. J., and Tinney, W. S.: Fistula Between the Esophagus and the Tracheobronchial Tree, M. Clin. North America **28**:1001-1007, 1944.

27. Bernstein, B. M.; Slater, S. R., and Grayzel, D. M.: Perforation of the Aorta into the Alimentary Tract: Case Report, Clinics **3**:447-449, 1944.

28. Collis, J. L.; Humphreys, D. R., and Bond, W. H.: Spontaneous Rupture of the Oesophagus, Lancet **2**:179, 1944.

Stricture.—Esophageal stenosis spontaneously perforating into the mediastinum caused death in a 7 month old baby who had accidentally ingested at the age of 1 month a drachm (about 2 Gm.), of lactic acid.[29] Crowe[30] analyzes the treatment of 57 patients with injuries caused by lye. Fifty-two (89 per cent) were under 5 years of age. Immediate lavage of the esophagus with weak acids and olive oil is recommended, followed by early prophylactic dilation with the Bokay method in all patients found by roentgenologic examination to have esophageal involvement. Of 13 such patients, 9 did not undergo stricture. Delay in treatment necessitates more drastic measures, accompanied by an 8 per cent mortality, but careful attention to the prevention of secondary stricture and long-continued dilation produced good results in the other 92 per cent.

Campbell[31] describes the case of a 14 year old boy in whom at the age of 5 years stricture of the lower part of the esophagus gradually developed, of unknown cause. Gastrostomy was performed. By the ingenious device of passing a needle threaded with silk through an esophagoscope placed in the stomach through the gastrostoma, the needle was also passed through the obstruction into another esophagoscope lying in the upper part of the esophagus and the thread thus brought out through the mouth. With this used as a guide, larger strings were gradually introduced and the area was canalized. Retrograde bouginage finally accomplished sufficient dilation to allow the passage of food and permit closure of the gastrostoma.

Scleroderma.—Richieri and d'Alotto[32] describe another instance of scleroderma and a short esophagus.

Ulcer.—The roentgenologic diagnosis is discussed, and 2 additional cases are reported.[33] Fatal perforation and bleeding from an esophageal ulcer occurred in a child following a burn.[34]

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29. Trainer, J. B.; Krippaehne, W. W.; Hunter, W. C., and Lagozzino, D. A.: Esophageal Stenosis Due to Lactic Acid, Am. J. Dis. Child. **69**:173-175 (March) 1945.

30. Crowe, J. T.: Poisoning Due to Lye: Value of Bokay Prophylactic Dilation in Prevention of Early Strictures of the Esophagus, Am. J. Dis. Child. **68**: 9-12 (July) 1944.

31. Campbell, A. A.: Canalization of Complete Oesophageal Stricture (Report of Case), Bull. Acad. Med., Toronto **18**:166-172, 1945; Canad. M. A. J. **52**:471-474, 1945.

32. Richieri, A., and d'Alotto, V.: Esófago corto y estómago torácico en una esclerodermia, Prensa méd. argent. **31**:2331-2333, 1944.

33. Lust, F. J., and Peskin, A. R.: Roentgenologic Diagnosis of Peptic Ulcer of the Esophagus, Am. J. Roentgenol. **52**:40-45, 1944.

34. Rankin, L. M.: Perforated Ulcer of Esophagus Following a Burn, Am. J. Surg. **67**:134-136, 1945.

Cardiospasm.—Hurst and Bassin [35] describe 11 cases of megaesophagus, which they diagnosed roentgenologically by means of mediastinal widening before giving a barium sulfate meal.

Three papers have appeared describing the pulmonary complications: abscess, aspiration pneumonitis, fibrosis and bronchiectasis. Megaesophagus with pulmonary complications may exist with slight, or indeed with no, symptoms referable to the esophagus.[36]

Field,[37] having studied the efficacy of amyl nitrite, glyceryl trinitrate and octyl nitrite in producing relaxation of the cardia, found that octyl nitrite possesses the following advantages: Its odor is more pleasant than that of amyl nitrite; it can be administered in an inhaler; it acts more rapidly than glyceryl trinitrate, and the inhaler dosage can be regulated more easily. [The reviewers have used octyl nitrite in a limited number of relatively early cases of cardiospasm, with encouraging results to date.]

Reports of the successful surgical treatment of cardiospasm continue to appear.[38]

Carcinoma.—The reported annual mortality from carcinoma of the esophagus is about 1,600 in England and Wales and about 2,000 in the United States. At autopsy 25 to 40 per cent of the carcinomas do not show metastases.[39] In 1,564 routine autopsies on male British West Indian and Panamanian Negroes, 35 (2.3 per cent) were found to have carcinoma of the esophagus, whereas in 591 autopsies on females the incidence was less than 1 per cent.[40] In a series of 3,048 unselected autopsies on adults, there were 599 cases of carcinoma, and in 19 (3.2 per cent) there was secondary involvement of the esophagus by carcinoma. In these 19 cases plus 7 others the primary sites were as follows: trachea or bronchus (8), stomach (7), larynx (4), breast (2), pancreas

35. Hurst, A., and Bassin, S.: Mega-Esophagus as a Cause of Mediastinal Widening, Am. J. Roentgenol. **52**:598-606, 1944.

36. Hawes, L. E., and Soule, A. B., Jr.: Pulmonary Changes in Cardiospasm, Am. J. Roentgenol. **53**:124-128, 1945. Bird-Acosta, I.: Pulmonary Suppuration Secondary to Cardiospasm, ibid. **52**:481-486, 1944. Weems, H. S.: Pulmonary Disease Associated with Mega-Esophagus, ibid. **52**:473-480, 1944.

37. Field, C. E.: Octyl Nitrite in Achalasia of the Cardia, Lancet **2**:848-851, 1944.

38. Maingot, R.: Extramucous Oesophagocardiomyotomy in Cardiospasm, Post-Grad. M. J. **20**:278-282, 1944. Ferrari, R. C., and Correa Iturraspe, M.: La esofagogastrostomía por vía torácica en el tratamiento del megaesófago, Prensa méd. argent. **31**:2089-2101, 1944.

39. Brock, R. C.: The Surgical Treatment of Carcinoma of the Oesophagus, Post-Grad. M. J. **20**:287-293, 1944.

40. Tomlinson, W. J., and Wilson, L. A., Jr.: Esophageal Carcinoma in British West Indian and Panamanian Negroes: A Study of the Incidence, Etiologic Factors and Pathologic Anatomy in Fifty Cases, Arch. Path. **39**:79-80 (Feb.) 1945.

(2), testes (1), mediastinal lymph nodes (1), undetermined (1).[41] Carcinoma constituted a complication of esophageal diverticulum in 2 (1.08 per cent) of 185 cases.[42]

Colledge [43] in discussing carcinoma of the upper third of the esophagus concludes that "operation is clearly justifiable in early, carefully selected cases, but these are very few and are likely to remain so, and both from the point of view of palliation and possibility of radical cure irradiation is far more frequently the method of choice." Several patients treated more or less successfully by surgical procedure and by irradiation are described. In a group of 38 patients treated palliatively by Patterson and Rouse [44] by means of intraesophageal and extraesophageal irradiation with dilation, 15 were benefited and 10 survived an average of fourteen and a half months after the diagnosis was made.

Holland [45] in an interesting discussion of multiple carcinoma presents a case in which there were four independent lesions, all cured, two by surgical and two by roentgen therapy. After five years there was no evidence of recurrence of the esophageal carcinoma treated by roentgen irradiation.

Lymphoma.—A case of cancerous lymphoma (clasmatocytic type) of the esophagus, the mediastinum and the retroperitoneal lymph nodes is presented.[46]

STOMACH

Review.—Mateer and his associates [47] have prepared an excellent analysis of the current literature on gastric disease, reviewing 124 articles.

Gastric Secretion.—Hollander's [48] excellent exposition of the various measures of acidity used at the present time by clinical and

41. Toreson, W. E.: Secondary Carcinoma of the Esophagus as a Cause of Dysphagia, Arch. Path. **38**:82-84 (Aug.) 1944.

42. Hoover, W. B.: Carcinoma Associated with Esophageal Diverticulum: Report of a Case, S. Clin. North America **25**:707-712, 1945.

43. Colledge, L.: Carcinoma in the Upper Third of the Oesophagus, Post-Grad. M. J. **20**:294-297, 1944.

44. Patterson, C. O., and Rouse, M. O.: The Treatment of Esophageal Neoplasms: Plea for Active Therapy Plus Minimum Confinement, South. M. J. **38**: 140-144, 1945. Patterson, C. O.; Rouse, M. O., and Bagwell, J. S.: Medical Management of Common Esophageal Disorders, Texas State J. Med. **40**:284-290, 1944.

45. Holland, C. A.: Multiple Carcinomas: A Case of Four Consecutive Primary Carcinomas with Apparent Cure, J. A. M. A. **128**:356-359 (June 2) 1945.

46. Cabot Case 31171, New England J. Med. **232**:481-484, 1945.

47. Mateer, J. G.; Baltz, J. I.; Comanduras, P. D.; Steele, H. H., and Brouwer, S.: Diseases of the Stomach: A Review of Current Literature, Gastroenterology **3**:360-379, 1944.

48. Hollander, F.: What Is p_H? An Explanation of the Various Measures of Acidity Employed in Gastroenterology, Gastroenterology **4**:497-508, 1945.

experimental workers in gastroenterology will interest all those not familiar with recent advances in chemical nomenclature. The advantages of the p_H system of notation are listed: First and foremost, it affords a way of representing and measuring acidities so low that they cannot be determined by titration methods, but which nevertheless are exceedingly important physiologically; second, many physiologic phenomena vary with the acidity, but the relation can be explained more simply in terms of the p_H units than of any of the other systems of notation; third, ionic concentrations other than of hydrogen can be expressed by a similar unit, the concentration of OH ions, for instance, being written p_{OH} and bearing in a solution a simple inverse relation to the concentration of hydrogen ions; finally, the p_H notation has given a convenient way of representing the minute numbers which describe acidities and alkalinities within the physiologic range.

Bull and Gray [49] discuss the mechanism of the formation of hydrochloric acid and suggest a new theory. A membrane lining the intracellular canaliculus of the parietal cell is thought to be impermeable to cations and at the same time permeable to anions. An organic acid, pyruvic or lactic, is produced in localized areas in the parietal cells. The anions of this acid are exchanged for chloride ions across the cation-impermeable membrane lining the canaliculus. The organic anion is destroyed by decarboxylation within the parietal cell, thus maintaining the necessary gradient of the organic anion.

Dyer and Kelly [50] compared, in 8 dogs in which gastric fistula had been produced, the secretory response to single injections of molecular equivalents of mecholyl and histamine. Their observations support the theory that mecholyl stimulates the secretion of both pepsin and acid, whereas histamine stimulates chiefly the acid and the volume of secretion. Grossman, Roth and Ivy [51] found that the output and the concentration of pepsin in response to caffeine are approximately the same as those in response to histamine for the first seventy minute period, but are sustained longer. If simultaneously caffeine is administered orally and histamine subcutaneously, pepsin is secreted in an amount greater than the sum of the amounts secreted in response to these drugs administered individually, provided a period

49. Bull, H. B., and Gray, J. S.: Secretion of Hydrochloric Acid by the Stomach, Gastroenterology **4**:175-182, 1945.

50. Dyer, H. M., and Kelly, M. G.: Gastric Function of Dogs After Stimulation with Acetyl-β-Methylcholine Chloride and Histamine Diphosphate, J. Nat. Cancer Inst. **5**:227-232, 1944.

51. Grossman, M. I.; Roth, J. A., and Ivy, A. C.: Pepsin Secretion in Response to Caffeine, Gastroenterology **4**:251-256, 1945.

longer than seventy minutes is studied. In cats and in man the gastric secretory response to histamine or to alcohol is greatly enhanced and prolonged after the administration of caffeine as compared with the output of hydrochloric acid or gastric juice provoked by histamine or alcohol before caffeine is administered. The response to histamine or alcohol and caffeine administered simultaneously is considerably greater than the sum of the individual responses.[52]

Gillman [53] compared the neutral red excretion and the acid secretion of 90 normal persons and found that, whereas the latter fluctuated considerably in the same subject, the excretion of neutral red remained remarkably constant. In a series of 300 persons considered to have "gastric dysfunction" the neutral red test appeared more sensitive. Nasio [54] reports that a 1 or 2 per cent solution of the hydrochloride of 2-benzyl-4,5-imidazoline (Priscol) given through a tube with 300 cc. of distilled water is a satisfactory stimulant of gastric secretion, although not so good as histamine; parenteral injection provides results similar to those with histamine.

It is surprising to find that nausea and retching inhibit even histamine-induced secretion in subcutaneously transplanted pouches and in vagally denervated pouches of dogs. Abdominal splanchnicectomy and lumbar sympathectomy do not abolish the effect.[55]

The failure of other workers to confirm the work of Andrus and his associates with regard to the inhibiting effect on gastric secretion of jejunal tissues transplanted to the stomach was noted last year. Andersen, Slutzky and Maertz [56] have now published another such failure, as have Kolouch, Dubus and Wangensteen,[57] and also Gross-

52. Roth, J. A., and Ivy, A. C.: The Synergistic Effect of Caffeine upon Histamine in Relation to Gastric Secretion, Am. J. Physiol. **142**:107-113, 1944.

53. Gillman, T.: A Critical Evaluation of the Neutral Red Excretion and Acid Secretion Tests of Gastric Function in the Normal and in Subjects with Gastric Disorders, Gastroenterology **3**:188-205, 1944.

54. Nasio, J.: A New Test for Gastric Function, Am. J. Digest. Dis. **11**:227-229, 1944.

55. Grossman, M. I.; Woolley, J. R.; Dutton, D. F., and Ivy, A. C.: The Effect of Nausea on Gastric Secretion and a Study of the Mechanism Concerned, Gastroenterology **4**:347-351, 1945.

56. Andersen, A. C.; Slutzky, B., and Maertz, R. W.: Effect on Gastric Secretion of Pedicle Jejunal Grafts in the Wall of the Stomach, Gastroenterology **4**:323-331, 1945.

57. Kolouch, F., Jr.; Dubus, A. T. S., and Wangensteen, O. H.: Symposium on Ulcer Problem: The Pedicled Jejunal Transplant onto the Gastric Wall; Evaluation of Its Effect upon Gastric Acidity and Failure of Such Transplants to Afford Protection Against Ulcer Provoked by Histamine in Beeswax, Surgery **17**:667-685, 1945.

man, Dutton and Ivy.[58] A jejunal pedicle graft implanted in the wall of the stomach or jejunal washings perfused through the stomach do not significantly alter the acid-secretory response of the stomach to stimulation with histamine in the dog.

In 19 patients with duodenal ulcer Dragstedt and his associates[59] observed that the night secretion averaged 820 cc., with free acidity between 24 and 82 clinical units; after transthoracic vagotomy the quantity decreased to an average of 415 cc., with free acidity between 0 and 61 clinical units. No significant difference in the response to histamine was noted. Using the balloon technic, they demonstrated hypermotility and hypertonicity of the empty stomach of the patient with peptic ulcer. Bilateral vagal section decreased the gastric tonus and the hunger contractions.[60]

Babkin and his associates[61] found that in dogs resection of the pyloric part of the stomach temporarily inhibits the action evoked by faradic stimulation of the vagus nerve and changes the character of the gastric juice from water-clear to mucoid. This work seems to support the view of those who think it essential to remove the pylorus in performing subtotal gastrectomy for peptic ulcer. [The reviewers are of the opinion that further controls and repetition of the experiments are needed.]

Acid introduced into the small intestine of the Pavlov pouch dog inhibits gastric secretion in response to a meal, provided an adequate degree of intestinal acidity is attained. The curve of gastric secretion seems dependent on the hydrogen ion concentration of the intestinal contents. Thus in experiments in which the intestial p_H was 3.0 or higher the rate of secretion was similar to that of control experiments. When the p_H was only 2.5, the secretion was depressed 50 per cent; almost complete inhibition resulted when the p_H was 2.0 or lower. A 0.9 per cent hydrochloric acid solution infused into the duodenum had no inhibitory effect. Histamine secretion is apparently not affected by

58. Grossman, M. I.; Dutton, D. F., and Ivy, A. C.: An Attempt to Confirm the Alleged Inhibitory Effect on Gastric Secretion of Jejunal Pedicle Grafts in the Wall of the Stomach, Surgery **17**:685-692, 1945.

59. Thornton, T. F.; Storer, E. H., and Dragstedt, L. R.: Supra-Diaphragmatic Section of Vagus Nerves and Gastric Secretion in Patients with Peptic Ulcer, Proc. Soc. Exper. Biol. & Med. **59**:140-141, 1945.

60. Storer, E. H.; Thornton, T. F., Jr., and Dragstedt, L. R.: Supra-Diaphragmatic Section of the Vagus Nerves and Gastric Motility in Patients with Peptic Ulcer, Proc. Soc. Exper. Biol. & Med. **59**:141-142, 1945.

61. Babkin, B. P.; Schaghter, M., and Nisse, R.: Further Studies on the Relationship Between the Vagal Secretory Function and the Chemical Phase of Gastric Secretion, Clinics **3**:494-505, 1944.

this regulatory mechanism.[62] Isotonic solutions of proteose, amino acids and sodium chloride failed to elicit secretion of gastric juice in fasting dogs when administered into the intestine in the absence of bile; bile alone was without effect; a moderate period of secretion was obtained after a latent period of one to two hours when proteose mixed with bile or hypertonic solution of amino acids or sodium chloride was placed in the intestine. Bile in the stomach stimulated secretion. Apparently the products of protein digestion alone do not elicit an intestinal phase of gastric secretion.[63]

Necheles and Olson,[64] observing the "corrosion" or "digestion" of metal cannulas used in the gastric pouches of experimental animals, found that plating with various metals was of little value and that brass cannulas were the most resistant.

Roentgen irradiation of the gastric region in dogs produced only minor anatomic changes in the mucosa and a transitory moderate anemia of the secondary type followed by an erythrocytotic phase after the cessation of treatment. The chief cells are the most sensitive; the parietal cells are more resistant.[65]

Hollander[66] points out that the mucus secreted in response to chemical irritation invariably contains large numbers of columnar epithelial cells with two or three other types, some of which may be goblet cells and may indicate the development of gastritis. It is suggested that these may be significant in cancer research.

Segal, Hodge, Watson and Scott[67] found that Amberlite IR-4, a polyamine-formaldehyde synthetic resin, produced elevation of the p_H of the gastric juice and inactivation of pepsin, the last action depending on the hydrogen ion concentration of the solution.

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62. Pincus, I. J.; Friedman, M. H. F.; Thomas, J. E., and Rehfuss, M. E.: A Quantitative Study of the Inhibitory Effect of Acid in Gastric Secretion, Am. J. Digest. Dis. **11**:205-208, 1944.

63. Beamer, W. D.; Friedman, M. H. F.; Thomas, J. E., and Rehfuss, M. E.: Factors Responsible for the Intestinal Phase of Gastric Secretion, Am. J. Physiol. **141**:613-618, 1944.

64. Necheles, H., and Olson, W. H.: Note on the "Digestion" of Metal in the Stomach, J. Lab. & Clin. Med. **29**:687-689, 1944.

65. Hueper, W. C., and de Carvajal-Forero, J.: The Effects of Repeated Irradiation of the Gastric Region with Small Doses of Roentgen Rays upon the Stomach and Blood of Dogs, Am. J. Roentgenol. **52**:529-534, 1944.

66. Hollander, F.: Physiology of Mucús Secretion, J. Nat. Cancer Inst. **5**:367, 1945.

67. Segal, H. L.; Hodge, H.; Watson, J. S., and Scott, M. W. J.: A Polyanine-Formaldehyde Resin: I. Its Effect upon the p_H of Acidified Solutions and the p_H and Pepsin of Gastric Juice in Vitro; II. Its Toxicity in Rats; Preliminary Feeding Tests, Gastroenterology **4**:484-496, 1945.

Gastric Motility.—Brody and Quigley [68] describe a method of measuring the motility of the pyloric sphincter in the unanesthetized dog by means of electromagnetic coils. Chronic experiments can be carried out. Crohn, Olson and Necheles [69] found that anesthetic drugs applied topically to the mucosa inhibited intestinal motility and tone but not gastric motility. Menendez Feros [70] reports his experiences in the electrocardiogastrographic testing of 112 patients. The hydrogen ion concentration of the intragastric electrolyte solution, the local changes of the gastric tissue and various other factors influence the graphs. The significance of this procedure cannot be determined at present.

Diaphragmatic Hernia.—The roentgenologic diagnosis of parasternal herniations is discussed.[71] Unusual cases include a congenital diaphragmatic hernia in a 5½ week old boy surgically repaired.[72] A 57 year old man with symptoms of acute obstruction was found at operation to have a diaphragmatic hernia with tortion, as well as complete inversion of the stomach with reversal of the position of the antrum and the doudenal cap, together with eventration of the diaphragm.[73]

Diverticulum.—Five more cases of diverticulum of the stomach are reported; gastroscopy aided in the diagnosis in 3.[74]

Congenital Pyloric Stenosis.—Vance [75] reports 27 cases in which congenital pyloric stenosis was treated by pyloromyotomy, with 1 death. In 95 per cent of the cases the pyloric tumor was felt in the right upper

68. Brody, D. A., and Quigley, J. P.: Application of the "Inductograph" to the Registration of Movements, Particularly of Body Structures Such as the Pyloric Sphincter, J. Lab. & Clin. Med. **29**:863-867, 1944.

69. Crohn, N.; Olson, W. H., and Necheles, H.: The Local Effect of Topic Anesthetic Drugs on the Motility of the Gastrointestinal Tract of the Human and the Dog, Surg., Gynec. & Obst. **79**:41-49, 1944.

70. Menendez Feros, J.: Study on the Electro-Cardiogastrographic Test: Its Possibilities in Differentiating Benign or Malignant Gastric Changes, Rev. Gastroenterol. **12**:99-110, 1945.

71. Ritvo, M., and Peterson, O. S., Jr.: Parasternal Diaphragmatic Hernia, Am. J. Roentgenol. **52**:399-405, 1944.

72. Wilson, A., and Trueman, K. R.: Repair of Congenital Diaphragmatic Hernia in an Infant, Canad. M. A. J. **52**:181-182, 1945.

73. Gardiner, H.: Diaphragmatic Hernia with Torsion of the Stomach and Acute Obstruction, Brit. M. J. **2**:114-115, 1944. Rosenfeld, D. H.: Unusual Type of Inversion of the Stomach Associated with Diaphragmatic Eventration and Other Anomalies, Am. J. Roentgenol. **52**:607-610, 1944.

74. Whitehouse, F., and MacMillan, J. M.: Gastric Diverticulum: Gastroscopic Observation of Two Cases, Gastroenterology **3**:13-22, 1944. Hunter, A. F.: Prepyloric Diverticulum of the Stomach Demonstrable Only by Pressure Roentgenograms, Am. J. Roentgenol. **52**:595-597, 1944. Frank, L. L.: Diverticulum of the Stomach: Case Report, ibid. **52**:510-513, 1944.

75. Vance, C. A.: Congenital Pyloric Stenosis, Tr. South. S. A. (1943) **55**:63-73, 1944.

quadrant, a little above the level of the umbilicus, at the outer border of the right rectus muscle. Dehydration was a prominent sign.

Gastroscopy and Gastritis.—Hardt[76] describes the advantage obtained by using a flexirigid gastroscope that gives an angle of visualization of 80 degrees without shifting of the instrument and an image approximately two and a half times as large as that with the flexible gastroscope. The instrument reduces the size of the blind areas in the stomach and causes the patient less discomfort. Hufford and Stonehouse[77] found that the greatest degree of flexion of the gastroscope occurs in the esophagus (10 degrees) and a lesser degree (5 degrees) in the fundus of the stomach. Whitehouse and MacMillan[78] suggest that the tip be colored green or some other identifiable color to prevent mistaking it for an ulcer.

Howard[79] in an excellent paper reviews his experience with the gastroscope and concludes that, while it rarely reveals an ulcer or a tumor not demonstrated by roentgenogram, gastroscopy is nevertheless valuable for the objective demonstration of the coarser gastric lesions. Chronic gastritis is an interesting finding that usually is not of great clinical importance. In a critique of gastroscopy as employed in 1,730 patients with 2,200 examinations, Tanner[80] reports that of 631 gastric ulcers no fewer than 159 were diagnosed by gastroscopy alone, having been missed by expert radiologists.

Analysis of 191 gastroscopic examinations of 143 patients disclosed 25 cases of superficial gastritis, 21 of hypertrophic gastritis, 7 of atrophic gastritis, 5 of gastric ulcer, 6 of postoperative gastritis and 77 of normal stomachs.[81] Tavares,[82] studying 100 consecutive pre-Pearl Harbor patients with dyspepsia, found that in the group with duodenal ulcer (24 patients) the gastric mucosa was normal in 12 and gastritis was present in 11. In his study of 14 patients with unexplained gross hemorrhage and no roentgenographic evidence, he found no gastric

76. Hardt, L. L.: The Flexi-Rigid Gastroscope, Gastroenterology **3**:508-511, 1944.

77. Hufford, A. R., and Stonehouse, G. G.: Orientation of the Gastroscope by Roentgenograms, Am. J. Digest. Dis. **12**:61-64, 1945.

78. Whitehouse, F. R., and MacMillan, J. M.: Visualization of Rubber Tip of Gastroscope: Differentiation from Gastric Ulcer, Gastroenterology **3**:103-105, 1944.

79. Howard, J. T.: Experiences with the Gastroscope over a Period of Six Years, South. M. J. **38**:293-302, 1944.

80. Tanner, N. C.: A Critique of Gastroscopy, Brit. M. J. **2**:849-851, 1944.

81. Loe, R. H., and Berger, E. H.: Gastric Diseases in Navy Personnel: A Study of One Hundred Ninety-One Gastroscopic Examinations, U. S. Nav. M. Bull. **43**:450-458, 1944.

82. Tavares, C. A.: Review of Gastroscopic Studies on One Hundred Consecutive Pre-Pearl Harbor Military Patients, War Med. **7**:304-308 (May) 1945.

lesion in 2, superficial gastritis in 6, atrophic gastritis in 1 and gastric ulcer in 2; in 3 the examinations were unsatisfactory.

Of 54 patients with benign gastric ulcer, 74 per cent had associated gastritis: superficial in 26 (48 per cent), hypertrophic in 6 (11 per cent), atrophic in 7 (13 per cent) and combined atrophic and superficial in 1 (2 per cent).[83]

Of 29 patients with pyloric obstruction due to duodenal ulcer, gastroscopic evidence of gastritis was found in 86 per cent, as compared with 62 per cent of patients without pyloric obstruction. Severe gastritis was noted six times as frequently in the group with stasis. Hence it is concluded that retention of gastric contents is associated with inflammatory change in the mucosa.[84]

Crohn[85] in discussing the present status of gastritis emphasizes the possible relation of antral gastritis to carcinoma. Vaughan[86] presents a roentgenologic and gastroscopic study of 3 cases in which this condition simulated carcinoma, describing his findings in detail. Hinkel[87] reports a case in which localized hypertrophic gastritis of the cardiac portion simulated benign tumor; Harris,[88] an instance of hypertrophic gastritis simulating carcinoma roentgenologically.

Bennett[89] in opening a discussion of gastritis points out that at the present time the diagnosis must rest principally on gastroscopy and that in his experience there is no recognizable symptom complex. Jones suggests "that superficial, hypertrophic and atrophic changes can be stages and phases of a single disease process—a nonspecific gastritis." Of 337 patients admitted for hematemesis and melena, about half were examined by gastroscopy, usually in the first week; only in 7 instances were these findings attributed to acute gastritis. Twenty-five per cent of 553 new patients with peptic ulcer and 158 with dyspepsia but without roentgenographic evidence of ulcer were examined by gastroscopy; in 10 of this group severe gastritis was thought compatible with the clinical symptoms. Hancock stresses the importance of experience in

83. Horner, J. L., and Scheff, H.: Incidence of Gastritis in Gastric Ulcer, Am. J. Digest. Dis. **12**:202, 1945.

84. Scheff, H.; Horner, J. L., and Kenamore, B.: Gastroscopic Observations in Pyloric Obstruction, Gastroenterology **3**:506-507, 1944.

85. Crohn, B. B.: Newer Advances in Our Knowledge of Gastritis, J. Mt. Sinai Hosp. **11**:75-82, 1945.

86. Vaughan, W. W.: Antral Gastritis: Roentgenologic and Gastroscopic Findings, Radiology **44**:531-542, 1945.

87. Hinkel, C. L.: Hypertrophic Gastritis Simulating Intramural Tumor of the Stomach, Am. J. Roentgenol. **53**:20-27, 1945.

88. Harris, C. M.: Hypertrophic Gastritis Simulating Carcinoma, Am. J. Surg. **68**:261-265, 1945.

89. Bennett, T. I.; Jones, F. A.; Hancock, P. E. T.; Gill, M., and Tanner, N. C., in Discussion on Gastritis, Proc. Roy. Soc. Med. **38**:81-90, 1944.

the diagnosis of hypertrophic gastritis, observing that in 1,400 gastroscopic examinations hypertrophic changes were diagnosed in 6 per cent of the first 300 and in only 0.66 per cent of the last 300. Normal areae gastricae may easily be interpreted as hypertrophic gastritis. Gill, examining the stomach after administration of histamine (effect on the mucosa) and insulin (effect on the nervous mechanism), found that in the normal stomach the mucosa becomes hyperemic and exudes a clear fluid which "trickles downward" in rivulets between the folds to form a pool on the greater curvature. The secretion rate averages 2.5 to 3.5 cc. per minute and the hydrochloric acid from 100 to 120 cc. In stomachs with hypertrophic gastritis the highest concentration of free hydrochloric acid was 160 to 200 cc., and the highest rate of secretion was 6 to 6.5 cc. per minute. This suggests that some forms of hypertrophic gastritis are accompanied by, or indeed perhaps merely represent, physiologic hyperactivity of the mucosa. In stomachs with atrophic gastritis there is pallor with diminution of secretory function, the rate of secretion being less than 1 cc. per minute. These findings suggest a degenerative process, although certainly in some cases regeneration with return of function can occur to some degree spontaneously. Gill suggests the terms "mucosal hypertrophy," "mucosal atrophy" and "mucosal hyperemia." Tanner considers that polypoid hyperplasia may be simulated by edema and congestion secondary to gastric stasis associated with duodenal ulcer. Of 1,730 patients with 2,200 gastroscopic examinations, only 4 per cent had gastritis of a severity considered compatible with clinical symptoms; 631 gastric ulcers were noted in the group.

Phlegmonous Gastritis.—Four cases of phlegmonous gastritis were encountered in 4,007 autopsies. The diagnosis was not made clinically. The disease is apparently a manifestation of sepsis with the agent localizing in the wall of the stomach rather than invading locally from the lumen.[90]

Corrosive Gastritis.—Meyer and Steigmann [91] report 4 cases of corrosive gastritis complicated by pyloric obstruction and point out that alkaline corrosives usually affect the esophagus, whereas acid corrosives most frequently result in pyloric obstruction. Three premature infants fed a milk mixture containing an excess of lactic acid died from acute hemorrhagic and gangrenous gastritis.[92]

90. Sachs, L. J., and Angrist, A.: Phlegmonous Gastritis as a Manifestation of Sepsis, Ann. Int. Med. **22**:563-584, 1945.

91. Meyer, K. A., and Steigmann, F.: The Surgical Treatment of Corrosive Gastritis, Surg., Gynec. & Obst. **79**:306-310, 1944.

92. Young, E. G., and Smith, R. P.: Lactic Acid: A Corrosive Poison; Report of Three Fatal Cases with Experimental Confirmation, J. A. M. A. **125**: 1179-1181 (Aug. 26) 1944.

Syphilis.—Voss [93] reports another instance of gastric syphilis thought clinically and at operation to be carcinoma. Gore and McCarthy [94] describe a 26 year old soldier with epigastric pain of one and a half year's duration, achlorhydria, serologic evidence of syphilis and a persistent prepyloric defect not appreciably influenced by four weeks of antisyphilitic therapy. After partial gastric resection the lesion was found to consist of a shallow mucosal ulceration with marked edema of the submucosa, thickening of the gastric wall, endarteritis, perivascular infiltration and nodular aggregates of epithelial cells unassociated with caseation or necrosis; giant cells were rare. The total picture, including the lack of endophlebitis, led the authors to reject the diagnosis of gastric syphilis in preference for localized Boeck's sarcoid. [To the reviewers the diagnosis of gastric syphilis seems much more probable.]

Aneurysm.—Taylor [95] reports a case of an anastomotic aneurysm of the left and right gastric arteries with rupture and fatal intraperitoneal hemorrhage.

Surgical Treatment.—In experiments performed on dogs, living omental patches satisfactorily sealed defects artificially produced in the stomach, whereas free grafts were susceptible to infection and the corrosive action of the digestive juice.[96]

The distress which is not infrequently felt in the upper abdominal area after partial or subtotal gastrectomy tends to decrease and disappear after the first postoperative year, as the stomach becomes adjusted to smaller meals and jejunal reservoirs are formed, according to Ingelfinger.[97] The importance of hypoproteinemia in retarding postoperative gastric evacuation has been stressed, but there is no direct correlation between the level of serum protein and the rate of gastric emptying. The poor evacuation is not due so much to an abnormal stoma as to a flattened or reversed gastroenteric pressure gradient. Fats, hypertonic solutions and hydrochloric acid entering the intestinal loops distal to the anastomosis delay emptying in the resected as well as in the normal stomach by relaxation of the gastric musculature and not by sphincteric contraction. In patients with gastrectomy the absorption of protein and of carbohydrate is unchanged but that of fat may be slightly impaired.

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93. Voss, F. H.: Syphilis of the Stomach: A Case Report, Rev. Gastroenterol. **12**:111-117, 1945.

94. Gore, I., and McCarthy, A. M.: Boeck's Sarcoid: Report of a Case Involving the Stomach, Surgery **16**:865-873, 1944.

95. Taylor, C. E.: Ruptured Anastomotic Aneurysm of Gastric Arteries: Case Report and Review of Literature, Am. J. Surg. **68**:258-268, 1945.

96. Price, P. B., and Lee, T. F.: Use of Omentum to Close Perforations of the Stomach, Arch. Surg. **50**:171-173 (March) 1945.

97. Ingelfinger, F. J.: The Late Effects of Total and Subtotal Gastrectomy, New England J. Med. **231**:321-327, 1944.

Bonorino and Castex [98] report that in a series of 43 gastrectomized patients they found roentgenologic evidence of decalcification in the pelvis and the spine in 39: slight in 7, moderate in 17, definite in 12 and conspicuous in 3. In the last group all the patients were over 60 years of age.

Benign Tumors.—The following interesting benign tumors have been described: an inflammatory cyst; an apple-sized solitary neurofibroma with a short broad pedicle; an enormous gastric schwannoma, which was surgically removed; a myoma with cancerous degeneration and ulceration; a benign myoma; a cancerous myoma with ulceration; a fibromyoma, and a papilloma.[99] Meissner [100] in an examination of 50 stomachs selected at random found 23 leiomyomas (46 per cent); they were not considered to be clinically significant.

Gastric Cancer.—(*a*) Incidence: Engel [101] notes that there are about 38,000 deaths annually from cancer of the stomach in the United States. There are 150,000 to 170,000 deaths annually from cancer in the Union of Soviet Socialist Republics, 30 to 40 per cent being due to gastric cancer.[102] Thorstad [103] observed no significant annual increase in the number of patients admitted because of gastric cancer in either the Harper Hospital or the City of Detroit Receiving Hospital. This is surprising, for the average age of the population continues to rise and the incidence of cancer increases with age.

(*b*) Genesis: Kirby [104] found no evidence of a significant lesion or tumor of the stomach in rats fed cholesterol heated to 300 C. for half an hour in amounts of 25 mg. per day for fifteen months, thus failing to confirm the assertion of Roffo.

98. Bonorino Udaondo, C., and Castex, M. R.: Gastrectomía y descalcificación esqueletica, Prensa méd. argent. **32**:3-18, 1945.

99. Horan, M. J., Jr., and Comfort, M. W.: Inflammatory Cyst of the Stomach Secondary to Cholecystic Disease: Report of Case, Proc. Staff Meet., Mayo Clin. **20**:237-241, 1945. Sanguily, J., and Leon Blanco, F.: Gastric Schwannoma: Report of a Large Intragastric Lesion Simulating a Bezoar, Surgery **17**:328-336, 1945. Aksel, A.: Solitary Neurofibroma in the Stomach, Brit. M. J. **2**:309, 1944. Dewey, E. B.: Benign Tumors of the Stomach, Am. J. Surg. **65**:233-237, 1944.

100. Meissner, W. A.: Leiomyoma of the Stomach, Arch. Path. **38**:207-209 (Oct.) 1944.

101. Engel, G. C.: Carcinoma of the Stomach and Its Problems, Clinics **4**: 13-26, 1945.

102. Bocharov, A. A.: Cancer of the Stomach, Am. Rev. Soviet Med. **1**:532-539, 1944.

103. Thorstad, M. J.: The Outlook on Carcinoma of the Stomach, Am. J. Surg. **64**:242-247, 1944.

104. Kirby, A. H. M.: Attempts to Induce Stomach Tumors: IV. The Effects of Cholesteryl Esters Heated to 300° C., and Cholesterol Heated to 430° C., Cancer Research **5**:129-134, 1945.

Strong [105] developed a strain of inbred mice in which methylcholanthrene produced tumors of diverse types. The descendants of these mice continued to show spontaneous development of gastric carcinoma. In the discussion of this tremendously important contribution the authors develop the concept "that the action of methylcholanthrene on the production of malignant lesions may be of a twofold nature: (1) the conversion of gastric mucosa into cancer; and (2) the production of a germinal mutation in a genetic entity which in some manner or other underlies certain morphologic or physiologic characteristics of gastric mucosa." The genetic aspect of this "inheritance of acquired characters" is well discussed by Jones, Little, Burns and Andervont.

Ivy [106] in an excellent and extensive review discusses the relations of gastric function and gastric cancer. The desirability of producing experimental chronic gastritis in animals is emphasized; the need for further study of the chemistry of mucus and its metabolism is pointed out, and numerous other facets of the problem of gastric cancer are noted. The paper should be read by all those interested in the subject. The discussion following it is likewise excellent. Stewart expresses the opinion that in general the concept that common chronic inflammatory lesions are involved in the causation of cancer is one from which pathologists have begun to steer away. Stout presents evidence to show that gastric cancer is more likely to develop in a stomach which shows atrophic changes in the presence of intestinal metaplasia, but he concludes that "whether these atrophic changes or the intestinal metaplasia have anything to do with the development of gastric cancer doesn't seem to me to have been proved at all." Stout did not find stages between metaplasia and the development of cancer. Warren expresses the opinion that "the significant type of chronic gastritis with respect to carcinoma is that in which there is epithelial alteration as well as purely inflammatory infiltration." Harvey and Stout refer to an interesting patient who underwent resection for a well differentiated fungating carcinoma and who twenty odd years later had a poorly differentiated and widely infiltrating tumor. Stewart hazards the wager that the greater the number of five year survivals, the more instances of this sort there will be. Warren and Meissner [107] present evidence to support the view that in chronic gastritis the exudative changes are not sig-

105. Strong, L. C.: Genetic Analysis of the Induction of Tumors by Methylcholanthrene: IX. Induced and Spontaneous Adenocarcinomas of the Stomach in Mice, J. Nat. Cancer Inst. **5**:339-362, 1945.

106. Ivy, A. C.: Gastric Physiology in Relation to Gastric Cancer, J. Nat. Cancer Inst. **5**:313-337, 1945.

107. Warren, S., and Meissner, W. A.: Chronic Gastritis and Carcinoma of the Stomach, Gastroenterology **3**:251-256, 1944.

nificant but that the epithelial changes when severe may be comparable to well recognized precancerous lesions occurring elsewhere in the body.

Stout [108] examined, by the multiple section method, 50 stomachs with carcinoma, 50 with gastric ulcer and 50 with duodenal ulcer. Mucosal atrophy was found in a larger number and tended to be more widespread in the stomachs with cancer. When there was juxtaposition of carcinoma and mucosal gland, it was impossible to tell whether the carcinoma was invading the gland or developing from the epithelial cells of the gland.

> . . . in occasional stomachs with carcinomas in them, multiple sections from various areas failed to show any epithelial changes at all in some while others showed only minimal changes. . . .
>
> It would seem, therefore, that while atrophy of the gastric mucosal epithelium and cyst formation are present to a greater degree and in larger numbers in stomachs with carcinomas than in comparable stomachs without cancer, the exact relationship between these two conditions remains undetermined.

Pertinent to this discussion is the observation that, of 43,021 consecutive autopsies, 293 were performed on persons over 45 years of age who had pernicious anemia and that in 36 of these gastric cancer was present, an incidence of 12.3 per cent, three times that of gastric carcinoma in persons of the same age group who did not have pernicious anemia.[109] In a roentgenologic study of 211 patients with pernicious anemia 17 (8.0 per cent) were found to have carcinoma and 15 (7.1 per cent) benign tumors, a total of 32, or 15.1 per cent. These observations constitute further evidence of an etiologic rather than an accidental relationship between pernicious anemia and gastric epithelial tumors.[110]

(*c*) Pathologic Aspects: Stout [111] calls attention to the carcinomas in which extension is chiefly centrifugal, the cells spreading along the plane of the gastric wall.

> . . . Grossly, these tumors thicken the mucosa and obliterate its folds, usually with shallow, bowl-shaped ulceration, or else they spread outward from the margins of a deep peptic ulcer . . . the regional-node metastatic rate in the group of 23 patients studied at the Presbyterian Hospital was only 39 per cent as compared with 75

108. Stout, A. P.: Gastric Mucosal Atrophy and Carcinoma of the Stomach, New York State J. Med. **45**:973-977, 1945.

109. Kaplan, H. S., and Rigler, L. G.: Pernicious Anemia and Carcinoma of the Stomach: Autopsy Studies Concerning Their Interrelationship, Am. J. M. Sc. **209**:339-348, 1945.

110. Rigler, L. G.; Kaplan, H. S., and Fink, D. L.: Pernicious Anemia and the Early Diagnosis of Tumors of the Stomach, J. A. M. A. **128**:426-432 (June 9) 1945.

111. Stout, A. P.: Superficial Spreading Type of Carcinoma of the Stomach, J. Nat. Cancer Inst. **5**:363, 1945.

per cent for the 123 gastric carcinomas resected during the same period. . . . there is reason to anticipate a 5-year cure rate of at least 50 per cent. Thus the superficial spreading carcinoma is one of the more curable forms of gastric cancer.

In necropsies of 243 persons with gastric cancer it was found that 9 per cent had multiple cancerous tumors; this is slightly higher than the general level, of 6.8 per cent. In necropsies of 476 persons with carcinoma of the large intestine the incidence of multiple cancerous lesions was 15 per cent.[112] A 60 year old man with coexistent primary carcinomas in the stomach and the rectosigmoid underwent successfully a double resection of the segments involved in spite of pulmonary tuberculosis.[113]

A primary carcinoma of the stomach produced a spontaneous gastrocolic fistula.[114] Metastatic involvement of the umbilicus in inoperable carcinoma has again been described.[115] In 1 case a diffuse lymphatic spread with metastases in the lungs and bone marrow gave an unusual roentgenogram of the chest and an eosinophilia of 27 per cent, creating a difficult diagnostic problem.[116]

Lowman and Kushlan[117] emphasize the importance of a careful pelvic examination of any female patient with intestinal symptoms, because of the incidence of ovarian metastases. The roentgenologic demonstration of an irritation of the small bowel may suggest the presence of generalized peritoneal carcinomatosis.

(*d*) Ulceration, Healing and Growth: Tumor tissue is exposed to peptic ulceration in the stomach only. Certain ulcerating gastric carcinomas may present the structure characteristic of peptic ulcer. This typical structure is attributed to peptic digestion of the carcinoma and adjacent tissue. In such ulcers there may be marked or even complete repair of the tissue defect. The scar of the ulcer may be covered by neoplastic mucosa or by a layer of epithelium perfectly normal in appearance. The disappearance of the ulcer crater as seen by roentgenogram does not prove, therefore, that the ulcer is of a benign nature. Likewise, the demonstration of neoplasm in one edge of an ulcer does not prove it to have been a benign ulcer with cancerous

112. Warren, S.: Multiple Cancers of the Human Gastrointestinal Tract, J. Nat. Cancer. Inst. **5**:375, 1945.

113. Pemberton, J. D., and Seefeld, P. H.: Simultaneous Primary Carcinomas of the Stomach and Sigmoid, Am. J. Surg. **66**:393-395, 1944.

114. Shirley, A. R.: An Unusual Gastrocolic Communication, Radiology **43**:588-590, 1944.

115. Lombardi, L. E., and Parsons, L.: Carcinoma of the Umbilicus Metastatic from Carcinoma of the Stomach, Ann. Int. Med. **22**:290-293, 1945.

116. Cabot Case 31242, New England J. Med. **232**:708-713, 1945.

117. Lowman, R. M., and Kushlan, S. D.: "The Krukenberg Tumors": The Roentgen and Gastroenterological Aspect of Secondary Ovarian Carcinoma, Gastroenterology **4**:305-322, 1945.

degeneration. Peptic ulceration and healing in primary carcinoma may well account for both phenomena. Eusterman, Fitzgibbon and Crohn present corroborative evidence.[118]

Of interest in this connection, and again illustrating the fact that in a case of gastric cancer a long history may not be indicative of so-called carcinomatous degeneration of a benign ulcer, is the reporting once more of a patient with a gastroenterostomy for duodenal ulcer in whom ten years later an independent cancer developed at the stoma.[119]

Schwartz[120] describes an exceedingly interesting case of a slow-growing carcinoma with which anemia was associated in consequence of its having metastasized to the bone marrow, as proved by biopsy. In spite of this, the patient, aided by blood transfusions, survived for three years. The gastric lesion, a small ulcerating carcinoma, was not found by roentgenographic or gastroscopic examination but was demonstrated at autopsy, near the cardia. Diffuse metastatic lesions were found in the liver and the bone marrow.

(*e*) Anemia: Of 122 patients with gastric cancer, 78 were found to have anemia: In 25 the anemia was macrocytic; in 35, normocytic, and in 18, microcytic; in most instances the anemia was normochromic.[121]

(*f*) Surgical Treatment: Of 143 patients with carcinoma of the stomach who died without surgical treatment, the lesion was confined to the stomach in 10 per cent and was theoretically curable by resection in 18 per cent.[122] Brunschwig[123] points out the feasibility and the advisability of extensive and widespread resection of perigastric tissues in an effort to reduce the metastatic spread of small early carcinomas.

In 323 patients subjected to operation at the Mayo Clinic there were 16 deaths, a hospital mortality rate of 5 per cent. Sixty per cent of all the patients whose condition was diagnosed as gastric cancer underwent operation. In 58 per cent of these the lesion was resected. The ratio of resections to the total number of patients was

118. Palmer, W. L., and Humphreys, E. M.: Gastric Carcinoma: Observations on Peptic Ulceration and Healing, Gastroenterology **3**:257-272, 1944.

119. Gonzales Rodriguez, A., and d'Alotto, V.: Cáncer de una neoboca en una gastroenterostomia por ulcus duodenal, An. Dispen. púb. nac. para enferm. d. ap. digest. **7**:117-125, 1944; Prensa méd. argent. **31**:1883-1886, 1944.

120. Schwartz, S. O.: Longevity with Metastatic Carcinoma of the Stomach, Ann. Int. Med. **22**:727-730, 1945.

121. Oppenheim, A.; Abels, J. C.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract, J. A. M. A. **127**: 273-276 (Feb. 3) 1945.

122. Metheny, D.: Modern Trends in Gastric Surgery Through 1943, West. J. Surg. **52**:476-480, 1945.

123. Brunschwig, A.: Radical Surgery for Gastric Cancer, J. Nat. Cancer Inst. **5**:365-366, 1945.

35 per cent, about 9 per cent higher than three years ago. There were 164 partial gastrectomies, with a mortality of 4.9 per cent; 17 total gastrectomies, with a mortality of 29.4 per cent; 25 palliative operations, with a mortality of 8 per cent, and 117 explorations, with a mortality of 0.9 per cent.[124] In Engel's series[125] 21 per cent were hopeless when first seen by the surgeon; an exploratory laparotomy alone was performed in 42 per cent; palliative gastroenterostomy was carried out in 20 per cent; radical operation was possible in only 17 per cent. The mortality for subtotal gastrectomies is reported as 3 to 5 per cent and that for total gastrectomies as 18 to 25 per cent.

According to Bocharov,[126] more than 50 per cent of the patients with gastric cancer admitted to the Central Oncological Institute in Russia from 1925 to 1934 were found incurable. Between 1932 and 1936 only 12.2 per cent of the patients admitted had operable lesions. In 767 subjected to laparotomy 294 resections were carried out. Of the total of 916 patients with gastric cancer, 21.7 per cent had been ill for less than three months. In this group only 31.6 per cent (of the 21.7 per cent) were candidates for radical surgical intervention. Twenty-five per cent of the group had had symptoms for three years or more. Fifty per cent of this group were subjected to radical surgical treatment. Of the 916 patients, 99 (about 11 per cent) had had symptoms of over ten years' duration. Neoplastic degeneration of benign ulcer was considered to have been responsible for 16.3 per cent of 1,020 cases of gastric carcinoma. No such degeneration of duodenal ulcer was noted in 2,376 operations for gastric ulcer and 820 operations for gastric carcinoma. Resection was feasible in only 30 per cent of the patients with carcinoma of the lesser curvature and in only 10 per cent of those with tumor of the cardia. Surgical intervention was most effective in the age group between 20 and 50. Of the 916 patients subjected to operation, radical surgical removal was possible in only 349 (38.1 per cent), with a mortality rate of 32 per cent—cachexia, pneumonia and peritonitis being the most frequent causes of death. In 164 patients with uncomplicated resections the mortality rate was 12 per cent. In 144 patients whose cases were complicated by metastases palliative resection was carried out, with a mortality rate of 43 per cent. In a third group, consisting of 53 patients in whom partial

124. Counseller, V. S.; Waugh, M., and Clagett, O. T.: Report of Surgery of the Stomach and Duodenum for 1943, Proc. Staff Meet., Mayo Clin. **19**:586-592, 1944.

125. Engel, G. C.: Carcinoma of the Stomach and Its Problems, Clinics **4**:13-26, 1945.

126. Bocharov, A. A.: Cancer of the Stomach, Am. Rev. Soviet Med. **1**: 532-539, 1944.

resection of the colon was done in addition to total or subtotal gastrectomy, the mortality rate was 66 per cent. One hundred and eighteen patients were followed from one to ten years. There were 13 five year and 5 ten year cures after palliative resection. Of the total group, 84.9 per cent died within two years, and only 7.2 per cent survived five years.

The proportion of patients with clinically inoperable cancer of the stomach was 42.3 per cent at the Harper Hospital and 76.6 per cent at the City of Detroit Receiving Hospital. Fifty-seven per cent of all patients with gastric cancer admitted to Harper Hospital were subjected to surgical treatment, in contrast with only 23.4 per cent at the City of Detroit Receiving Hospital. At Harper Hospital gastroenterostomy was performed in 10.8 per cent of the entire series of patients, while at the City of Detroit Receiving Hospital only 3.7 per cent were treated thus. Gastrectomy was performed in 19.4 per cent of the patients at Harper Hospital and in 9.8 per cent of those at the Receiving Hospital. The mortality rate for gastrectomy at Harper Hospital during 1941 and 1942 was 29.0 per cent—a definite improvement over other years. Finally, no evidence was found to indicate that there had been a marked improvement in either diagnosis or treatment of early carcinoma of the stomach during this fifteen year period. It is assumed that these contrasting figures reflect the fact that the Harper Hospital is a private institution and the City of Detroit Receiving Hospital a municipal one. The private patients report to the physician earlier than do the indigent; thus an earlier diagnosis is made, more patients are subjected to laparotomy and more resections are possible. One wonders, however, if this is the complete explanation.[127]

Custer[128] reports the follow-up of 96 patients with gastric cancer which was considered operable in a group of 141: Two died during operation (2.03 per cent); 9 died of fatal postoperative complications (9.37 per cent); 23 did not survive over three years (35.34 per cent); 36 (37.59 per cent) died in the three to five year interval; 26 survived five years (27.06 per cent; 18 were alive after eight years (18.75 per cent). In contrast with this, 28 patients who refused operation were all dead in three years. Lund[129] reports a partial gastrectomy performed in 1909 which the patient survived for thirty-five years. Allen,

127. Thorstad, M. J.: The Outlook on Carcinoma of the Stomach, Am. J. Surg. **64**:242-247, 1944.

128. Custer, W. C.: Survival After Gastric Resection in Carcinoma of the Stomach, Surgery **17**: 510-511, 1945.

129. Lund, F. B.: Partial Gastrectomy for Carcinoma Thirty-Five Years Ago, New England J. Med. **232**: 562-564, 1945.

in discussing this paper, refers to Parsons' study showing a five year curability rate of about 20 per cent for gastric carcinoma.

Jones and Kehm [130] in a follow-up report of 8 consecutive total gastrectomies states that all the patients are living, with postoperative periods varying from six to eighteen months. Lahey and Marshall [131] report 73 total gastric resections, with 24 (33 per cent) postoperative deaths. The abdominal approach is considered safer than the transpleural. Fourteen of the operative deaths were due to peritonitis and 10 to medical complications involving the heart and the lungs. In 23 survivors ultimately dying of recurrent disease the average postoperative duration of life was eighteen months. Twenty-six patients have had no recurrence for periods ranging from six months to six years. The mortality rate in 28 operations performed in the past two years was 18 per cent. Sweet [132] reports that 127 patients with carcinoma of the stomach or the esophagus were operated on by the transthoracic approach from 1939 to November 1944 at the Massachusetts General Hospital. Of 85 in whom the stomach or the lower part of the esophagus and the cardia were involved, 24 were found to have inoperable lesions. Of 42 midesophageal carcinomas, 17 were inoperable; 25 were resected, but only 11 of the 25 allowed high intrathoracic esophagogastric anastomosis. Fourteen were subjected to the Torek operation (prior to 1944). Of the 42 midesophageal carcinomas, 59.5 per cent were resectable. Partial gastrectomy with low esophagogastric anastomosis was carried out in 43 patients; total gastrectomy was performed in 18; partial gastrectomy with a high esophagogastric anastomosis in 11. In these three groups the mortality rates were, respectively, 18.6, 38.9 and 27.3 per cent. For the entire series of 72 patients undergoing partial or total esophagogastric resection the mortality was 25 per cent. Additional cases are reported by others.[133]

[To the reviewers these somewhat confusing statistics seem to indicate a trend toward earlier diagnosis and a higher incidence of partial and of total gastrectomy. In general, the mortality rates have

130. Jones, T. E., and Kehm, R. W.: Total Gastrectomy: Report of Eight Cases, Surg., Gynec. & Obst. **80**: 534-538, 1945.

131. Lahey, F. H., and Marshall, S. F.: Indications for, and Experiences with, Total Gastrectomy Based upon Seventy-Three Cases of Total Gastrectomy, Tr. South. S. A. (1943) **55**: 12-32, 1944.

132. Sweet, R. H.: Transthoracic Resection of the Esophagus and Stomach for Carcinoma: Analysis of the Postoperative Complications, Causes of Death and Late Results of Operation, Ann. Surg. **121**: 272-284, 1945.

133. Griswold, R. A.: Transthoracic Gastrectomy for Unusual Lesions of the Stomach, Ann. Surg. **121**: 600-619, 1945. Milanes, F.; Vega, T.; Morales, E.; Rodriguez, A., and Diaz, R. A.: Total Gastrectomy: Clinical and Physiopathological Study, Gastroenterology **3**: 380-387, 1944.

gradually decreased and the survival rates increased. On the basis of the present evidence, however, the outlook in the presence of gastric cancer is still discouraging. Many lives will be lengthened by early diagnosis and operation, but physicians will never be able to look on a surgical procedure as a "cure" for this disease. It seems evident that in the majority of patients metastases occur before the symptoms are sufficiently definite to arouse the attention of the patient and to induce him, regardless of his economic status, to consult a physician. The diagnostic problems are, as a rule, not great. The difficulty is in the nature of the disease, its tendency toward early spread and the inability of the surgeon to cope successfully with the metastases.]

(*g*) Acute Perforation: The incidence of perforation varies from 2.8 to 6.0 per cent. Bisgard and Overmiller,[134] in reporting a recovery, review the literature and find that in 115 cases the mortality following simple closure is 80 per cent.

(*h*) Hodgkin's Disease: Of 213 patients with Hodgkin's disease, 24 had primary gastrointestinal symptoms, and yet only 9 had lesions of the digestive tract. During the course of the disease, abdominal symptoms were also frequent but were not due to local involvement. In 6 of 174 cases the disease was primary in the digestive tract; indeed, it was confined almost entirely to this tract. The stomach was involved in 3, the cecum in 2 and the duodenum and the esophagus each in 1. Multiple involvement of the digestive tract was not observed. None of the lesions were suspected during life. In cases of sarcoma, on the other hand, multiple involvement of the gastrointestinal tract is common.[135]

(*i*) Lymphosarcoma: Miller and Eusterman [136] describe a patient with Mikulicz's syndrome who presented a peculiar pulmonary and gastric involvement. The gastroscopic appearance of the latter was suggestive of lymphoma. Biopsy of a nodule in the right orbit disclosed lymphosarcoma of a low grade. All the lesions responded beautifully to roentgen therapy. This observation leads the authors to question the assumption that the process in Mikulicz's original case was benign and self limited.

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134. Bisgard, J. D., and Overmiller, W.: Emergency Gastrectomy for Acute Perforation of Carcinoma of the Stomach with Diffuse Soiling of the Free Peritoneal Cavity, Tr. Am. Surg. A. **62:** 526-530, 1944; Ann. Surg. **120:** 526-530, 1944.

135. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's Disease: IV. Involvement of Certain Organs, New England J. Med. **232:** 547-559, 1945.

136. Miller, J. R., and Eusterman, G. B.: Mikulicz's Syndrome: Report of a Case with Associated Pulmonary and Gastric Lesions, Proc. Staff Meet., Mayo Clin. **19:** 425-431, 1945.

Rafsky, Katz and Krieger,[137] reporting 11 cases of lymphosarcoma of the stomach, proved to be such, and another, probable case, failed to find any characteristic history. In 50 per cent there was a history simulating that of peptic ulcer. In 33 per cent the physical examination revealed an abdominal mass; in 33 per cent the correct diagnosis was made by roentgenogram; in 50 per cent the lesion simulated carcinoma. The gastric acidity varied widely. The gastroscopic appearance of the 4 stomachs examined was not characteristic of cancerous involvement: There was striking hypertrophy of the mucosal folds; the mucous membrane appeared swollen and edematous, but it was intact; later in the disease flattened ulcerated areas were seen on the crests of the folds. The diagnostic difficulties in such cases are further illustrated by a lesion not seen roentgenologically and not positively identified gastroscopically because of the similarity of carcinoma, lymphoma and gastritis. Subtotal gastrectomy was performed. The authors suggest, however, that in the case of an inoperable gastric tumor radiation therapy may be indicated in the hope that the lesion may be a radiosensitive lymphoma.[138] A lymphosarcoma with metastases and chyliform ascites is reported.[139]

Peptic Ulcer.—(*a*) Incidence: Morris and Titmuss,[140] in analyzing the mortality from peptic ulcer as revealed in the reports of the Registrar General for England and Wales, found that in men the mortality is steadily rising, the process having been accelerated in the period from 1939 to 1941, whereas in women the mortality has been falling except for a slight reversal of the trend in the period from 1939 to 1941. The important increase in the death rate of both gastric and duodenal ulcer is in men over 45. The mortality from gastric ulcer is heavier than that from duodenal ulcer, the pattern resembling that of gastric cancer. The mortality is higher in the Greater London areas and lowest in the rural sections. There is no significant class bias, although in old age deaths are heavier among the well-to-do. The authors find it "hard to resist the conclusion that urban life nowadays is an ideal soil for the flowering of the ulcer temperament." Carslaw,[141] in Glasgow,

137. Rafsky, H. A.; Katz, H., and Krieger, C. I.: Varied Clinical Manifestations of Lymphosarcoma of the Stomach, Gastroenterology **3**: 297-305, 1944.

138. Paul, W. D., and Parkin, G. L.: Lymphosarcoma of the Stomach: A Gastroscopic Report, Gastroenterology **3**: 214-217, 1944.

139. Martin, L.; Pereira Torres, R. A., and Lazzar, A.: Linfosarcomatosis gástrica, Prensa méd. argent. **32**:474-475, 1945.

140. Morris, J. N., and Titmuss, R. M.: Epidemiology of Peptic Ulcer: Vital Statistics, Lancet **2**: 841-845, 1944.

141. Carslaw, J.: A Study of the Number of Cases Treated in the Western Infirmary of Glasgow During Forty-Six Years (1897 to 1942), Glasgow M. J. **24**: 183-188, 1944.

found over a period of forty-five years an "appalling increase" in duodenal ulcer, both perforated and unperforated, especially in men.

The incidence of acute perforation during a twenty year period (1924 to 1943) in West Scotland increased progressively up to 1938, rose impressively in 1940-1941 and then decreased. The 1940-1941 rise was not correlated with air raids. The authors suggest that, in addition to anxiety about the war situation, overwork and perhaps undernutrition may have exerted an influence. The sex ratio underwent little variation. The lesion was rare in childhood, rose infrequently in adolescence and attained a maximum between the ages of 30 and 40 years. Perforations were uncommon in August, September and October and common in December. They were less frequent on Sundays and Mondays and were unduly common between 3 p.m. and 6 p.m.[142]

(*b*) Etiologic Factors: Herbut[143] reports that in 5 patients acute peptic ulcer developed after distant operations, but no evidence is presented to indicate a casual relationship.

Koch and Fischer[144] describe a patient who twenty-three days after a severe burn of the leg died from perforation of an acute ulcer of the duodenum.

Gray[145] describes 29 patients in whom trauma apparently resulted in the formation of a peptic ulcer.

(*c*) Experimental Observations: The incidence of gastrojejunal ulcer in dogs with complete intragastric regurgitation of the contents of the duodenal loop is dependent on the length of the afferent duodenojejunal loop, since only 1 ulcer developed in 11 dogs with a short loop (8 to 15 cm.) and 5 in 6 dogs with a long loop. Four of these died of generalized peritonitis secondary to perforation.[146] In a study of gastric resection three series of experiments were carried out in 22 dogs. Eleven were subjected to a 75 per cent resection with a short (12 to 15 cm.) duodenal loop; in none did ulcer develop in response to stimulation with "histamine in beeswax." In the second series

142. Illingworth, C. F. W.; Scott, L. D. W., and Jamieson, R. A.: Acute Perforated Peptic Ulcer: Frequency and Incidence in the West of Scotland, Brit. M. J. **2**:617-620 and 655-658, 1944.

143. Herbut, P. A.: Acute Peptic Ulcers Following Distant Operations, Surg., Gynec. & Obst. **80**: 410-415, 1945.

144. Koch, V. W., and Fischer, W. A.: Duodenal Ulcer with Perforation Following a Cutaneous Burn: Report of a Case, Ann. Int. Med. **22**: 719-727, 1945.

145. Gray, I.: Trauma in Relation to Peptic Ulcer, New York State J. Med. **45**: 887-892, 1945.

146. Merendino, K. A.; Varco, R. L.; Litow, S.; Kolouch, F., Jr.; Baronofsky, I., and Wangensteen, O. H.: I. Stomal Ulcer Attending Complete Intragastric Regurgitation Influenced by Length of Afferent Duodenojejunal Loop, Proc. Soc. Exper. Biol. & Med. **58**:222-225, 1945.

(7 dogs) a long afferent duodenal loop was used (27 to 78 cm.); after histamine stimulation a gastrojejunal ulcer resulted in each animal. In the last series, 4 dogs with long afferent duodenojejunal loops received no histamine after gastric resection, but 2 showed, nevertheless, spontaneously developed, perforated gastrojejunal ulcers.[147] In 12 gastrojejunostomized dogs the incidence of ulcer varied according to the length of the duodenojejunal loop—from 16.2 per cent when the loop was short to 66.6 per cent when it was long.[148] Small gastric resections (25 to 50 per cent) when there is no afferent loop (Billroth's operation I) are accompanied by a high incidence of histamine-invoked ulcers, whereas when a three-quarter resection is done, stomal ulcer cannot be produced with histamine. These experiments all seem to emphasize in ulcer formation the ratio between the quantity of acid gastric juice and the quantity of neutralizing intestinal content, or the net peptic activity.[149]

Driver, Chappell and Carmichael[150] studied the digestion of the mucosa in different portions of the jejunum in dogs, using varying concentrations of pepsin in tenth-normal hydrochloric acid, and found that "the more distal loops of the gut seemed to be more susceptible to the action of pepsin in hydrochloric acid than the more proximal segments." A rise in hydrostatic pressure resulted in an impressive increase in the extent of peptic digestion and a decrease in the time required for perforation. At 45 cm. pressure the average time for perforation was found to be three hundred minutes; at 90 cm. pressure, eighty-two minutes, and at 135 cm. pressure, only forty-one minutes.[151]

Conversely, the time required for perforation was lengthened by raising the intra-abdominal pressure. Under atmospheric pressure the interval of time was eighty-two minutes; with 20 cm. of saline solution it was increased to one hundred and sixteen minutes, and at 45 cm. pres-

147. Merendino, K. A.; Lannin, B. G.; Kolouch, F, Jr.; Baronofsky, I.; Litow, S. S., and Wangensteen, O. H.: Length of Afferent Duodenojejunal Loop in Gastric Resection: A Factor in Stomal Ulcer, Proc. Soc. Exper. Biol. & Med. **58**:226-230, 1945.

148. Kolouch, F., Jr.; Castellanos, M.; Dubus, A. T. S.; Baronofsky, I., and Wangensteen, O. H.: III. Mechanism of Stomal Ulcer Is Related to Length of Afferent Duodenojejunal Loop, Proc. Soc. Exper. Biol. & Med. **58**: 275-280, 1945.

149. Baronofsky, I.; Lannin, B. G.; Sanchez-Palomera, E., and Wangensteen, O. H.: Billroth I, Gastric Resection: Extent Necessary to Protect Against Histamine-Provoked Ulcer, Proc. Soc. Exper. Biol. & Med. **59**: 229-231, 1945.

150. Driver, R. L.; Chappell, R. H., and Carmichael, E. B.: Effect of Concentration of Pepsin and the Differential Susceptibility of Jejunal Segments in Experimental Jejunal Ulcers in the Dog, Am. J. Digest. Dis. **12**: 166-167, 1945.

151. Driver, R. L.; Chappell, R. H., and Carmichael, E. B.: Effect of Hydrostatic Pressure on the Experimental Production of Ulcers, Am. J. Digest. Dis. **12**: 168-169, 1945.

sure, to one hundred and eighty-five minutes.[152] The proteolytic enzymes rennin, trypsin and erepsin under a hydrostatic pressure of 90 cm. of water produced necrosis, rennin being the most active of the three. The average time required to produce perforation with tenth-normal hydrochloric acid alone was about 50 per cent more than was required with rennin and tenth-normal hydrochloric acid. Neither steapsin nor amylopsin caused necrosis.[153]

Nasio[154] found that "cinchophen ulcers" occur at an average of thirteen days after the administration of the drug has begun. During the first five days congestive-hemorrhagic gastroenteritis is present, followed by erosive gastritis, which diminishes when the peptic ulcer appears. The administration of 10 to 20 mg. of napthoquinone did not prevent the production of ulcer, nor did 180,000 to 360,000 units of vitamin A.[155] Nicotinic acid seemed to favor ulcer formation and produced, when given alone, an inflammation of the gastrointestinal tract.[156]

Typical peptic ulcers could be produced in 40 per cent of guinea pigs and cats by daily administration of 100 mg. of caffeine in beeswax. In pouch dogs the injection of 1,200 mg. of caffeine (alkaloid) in aqueous solution increased the acidity and the volume of secretion in two thirds of the experiments. A prolonged definite increase of secretion was observed in dogs given 2,500 mg. of caffeine (alkaloid) in beeswax for four consecutive days. In human subjects, 2 cups of black coffee increased gastric secretion in 73 per cent of the tests; caffeine and sodium benzoate U. S. P. (300 to 976 mg.) evoked a marked response in 90 per cent of the tests.[157] Roth and Ivy[158] present evidence that caffeine-

152. Chappell, R. H.; Driver, R. L., and Carmichael, E. B.: Increased Intra-Abdominal Pressure as a Means of Inhibiting Perforations Due to Pepsin Solutions Under Hydrostatic Pressure in the Small Intestines of Dogs, Am. J. Digest. Dis. **12:** 169-171, 1945.

153. Driver, R. L.: Ulcer Production in Intestines of Dogs by Various Enzymes Under Hydrostatic Pressure, Proc. Soc. Exper. Biol. & Med. **59:** 281-282, 1945.

154. Nasio, J.: La úlcera péptica experimental cincofénica: I. Producción y patología, Prensa méd. argent. **31:**2659-2669, 1944.

155. Nasio, J.: Acción de la vitamina K sobre la úlcera péptica cincofénica, Prensa méd. argent. **32:** 476-477, 1945; Acción de algunas vitaminas sobre la úlcera péptica cincofénica del perro, ibid. **32:** 270-272, 1945.

156. Nasio, J.: Acción del factor PP sobre la úlcera péptica experimental cincofénica, Prensa méd. argent. **32:** 720-722, 1945.

157. Merendino, K. A.; Judd, E. S.; Baronofsky, I.; Litow, S. S.; Lannin, B. G., and Wangensteen, O. H: Influence of Caffeine on Ulcer Genesis: Experimental Production of Gastric Ulcer in Guinea Pigs and Cats with Caffeine, Together with a Study of Its Effect upon Gastric Secretions in Dog and Man, Surgery **17:** 650-666, 1945.

158. Roth, J. A., and Ivy, A. C.: The Pathogenesis of Caffeine-Induced Ulcers, Surgery **17:**644-649, 1945.

induced ulcers result from the proteolytic action of acid and pepsin on a gastric mucosa rendered more susceptible by "vascular" and "cellular" changes. The sequence of events is thought to be: vasodilatation and engorgement, vascular stasis, local anoxia, increased capillary permeability, transudation, extravasation of blood elements and decreased cellular nutrition.

Roth, Ivy and Atkinson [159] summarize their work on caffeine-induced "peptic" ulcer as follows: 1. Caffeine in relatively large doses causes acute and subacute ulceration of the gastric mucosa in cats. 2. Caffeine (80 to 250 mg.) stimulates gastric secretion in man and the cat but not in the dog. 3. Caffeine acts synergistically with histamine or alcohol in the stimulation of gastric secretion in man and the cat. 4. Caffeine-containing beverages stimulate gastric secretion in man. Coffee substitutes produced by roasting cereal contain secretagogues which stimulate gastric secretion in man. Coffee stimulates gastric secretion because of its caffeine content and because of other secretagogues (natural products of roasting or irritant volatile oils). 5. Caffeine and caffeine-containing beverages provoke a prolonged increase in the total output of acid in patients with peptic ulcer. 6. Five of a group of 50 normal, i. e., asymptomatic, human subjects responded to the caffeine test meal like patients with ulcer. Three of the 5 subsequently began to experience the ulcer type of distress, and 1 of these at the time of writing had an ulcer, as demonstrated by roentgenogram. 7. The evidence indicates that excessive use of caffeine-containing beverages may contribute to the genesis of "peptic" ulcer in the ulcer-susceptible person and will render the therapeutic management of the condition more difficult.

(*d*) Ulcer, Gastritis and Psychoneurosis: Among 45 consecutive patients with complaints referable to the upper part of the gastrointestinal tract 23 had roentgenologic evidence of duodenal ulcer. In these gastritis (diagnosed by gastroscopy) and psychoneurosis were not common. Of the other 22 patients, without roentgenologic evidence of ulcer, 80 per cent had some degree of psychoneurosis and 50 per cent had some degree of gastritis.[160]

(*e*) Analysis of Gastric Content: In 200 patients with digestive disturbances encountered in an army hospital in the Pacific war zone

159. Roth, J. A.; Ivy, A. C., and Atkinson, A. J.: Caffeine and "Peptic" Ulcer: Relation of Caffeine and Caffeine-Containing Beverages to the Pathogenesis, Diagnosis and Management of "Peptic" Ulcer, J. A. M. A. **126**:814-820 (Nov. 25) 1944.

160. Montgomery, H.; Schindler, R.; Underdahl, L. O.; Butt, H. R., and Walters, W.: Peptic Ulcer, Gastritis and Psychoneurosis Among Naval Personnel Suffering from Dyspepsia, J.A.M.A. **125**: 890-894 (July 29) 1944.

by Rush, the odds in favor of a diagnosis of peptic ulcer increased as the free hydrochloric acid of specimens obtained from fasting stomachs rose above 50 to 75 units and as the volume of the content of the fasting stomachs rose above 120 cc.[161]

(*f*) Location: Of 960 benign gastric ulcers, only 20 (4.8 per cent) were located on the posterior wall.[162]

Blum [163] adds a case of benign ulcer of the greater curvature to the 15 proved cases recorded in the literature.

(*g*) Medical Treatment: Alvarez [164] stresses the prophylactic importance of providing frequent feedings and antacid therapy during periods of emotional stress. Similarly, Rehfuss,[165] in a paper entitled "The Ulcer Life," emphasizes again the well known tendency of ulcer to recur and the importance of continuing treatment throughout the periods of quiescence. The patient must follow the rules as long as he lives. Emery [166] gives an equally broad and yet detailed outline of the philosophy, the theory and the practice of the treatment of the individual patient with peptic ulcer. Morlock [167] stresses the importance of acid in the formation of ulcer and points out the importance of patient cooperation. Collins [168] likewise emphasizes the role of nonabsorbable antacids, principally aluminum hydroxide gel, and the importance of supervised management, extending over the lifetime of the patient. A new compound, the basic aluminum salt of aminoacetic acid, has been found 42 per cent more efficient as an antacid than dried aluminum hydroxide gel U. S. P.[169] Rossett and Flexner,[170] using a simplified

161. Rush, A.: Fractional Gastric Analysis: A Simplified Technic with Interpretation of Results, M. Clin. North America **28**: 1516-1526, 1944.

162. Bonorino Udaondo, C.; d'Alotto, V., and Maciel, J. R.: Ulceras de la cara posterior del estómago, An. Dispen. pub. nac. para enferm. d. ap. digest. **7**: 335-349, 1944; Prensa méd. argent. **31**: 2213-2219, 1944.

163. Blum, S. D.: Peptic Ulcer of the Greater Curvature of the Stomach, Am. J. Roentgenol. **52**:291-297, 1944.

164. Alvarez, W. C.: How to Avoid Flare-Ups of Peptic Ulcer, J.A.M.A. **125**: 903-904 (July 29) 1944.

165. Rehfuss, M. E.: The Ulcer Life, Clinics **3**: 480-493, 1944.

166. Emery, E. S., Jr.: The Treatment of the Patient with an Uncomplicated Peptic Ulcer, M. Clin. North America **28**: 1164-1172, 1944.

167. Morlock, C. G.: The Present Status of the Treatment of Uncomplicated Duodenal Ulcer, Proc. Staff Meet., Mayo Clin. **19**: 449-455, 1944.

168. Collins, E. N.: Use of Aluminum Hydroxide and Other Nonabsorbable Antacids in Treatment of Peptic Ulcer, J.A.M.A. **127**: 899-901 (April 7) 1945.

169. Krantz, J. C., Jr.; Kibler, D. V., and Bell, F. K.: The Neutralization of Gastric Acidity with Basic Aluminum Aminoacetate, J. Pharmacol. & Exper. Therap. **82**: 247-253, 1944.

170. Rossett, N. E., and Flexner, J.: The Effect of Certain Antacids in Man Measured by a Simplified Method for the Continuous Recording of Gastric p_H, Ann. Int. Med. **21**: 119-121, 1944.

method for the continuous recording of the p_H of the content of the human stomach, have again shown that milk and calcium carbonate, aluminum hydroxide gel U. S. P. and magnesia magma U. S. P. are long-acting antacids. Further emphasizing the "acid-pepsin" factor in peptic ulcer, Winkelstein [171] successfully used the continuous intragastric drip of milk-sodium bicarbonate or aluminum hydroxide gel in treatment of 60 patients whose gastric ulcers were considered refractory to the Sippy program. A well illustrated paper on gastric ulcer as treated by duodenal feeding, gastroscopically controlled, is presented by Freeman.[172]

Ivy [173] found that, whereas ulcer developed in 98 per cent of 114 Mann-Williamson control dogs in an average of thirty-eight months, 76 per cent of 25 such dogs treated daily for one year with enterogastrone did not show development of jejunal ulcer. Enterogastrone was given by injection to 43 patients. With 5 the injections were stopped because the patients complained of local pain. The immediate effects were not so rapid and did not produce as complete relief as those of strict ulcer management. The number of recurrences of ulcer distress in a group of 21 patients was reduced for a six month period from an anticipated 21 to 4. The author concludes that the preliminary results are sufficiently encouraging to warrant further study.

(*h*) Surgical Treatment: Heuer and associates [174] have published a book entitled "The Treatment of Peptic Ulcer Based upon Ten Years Experience at the New York Hospital." It cannot be reviewed here, but those interested will find that it illustrates clearly the trends of the past decade.

Eliason and Stevens [175] analyze the data on a consecutive series of 100 patients with peptic ulcer who were subjected to operation, with a mortality of 2 per cent. The indications for operation were perforation in 17 per cent, obstruction in 17 per cent, severe hemorrhage in 28 per cent and intractability, based on repeated recurrences of pain, in 55 per cent—which reads 69 per cent if one includes some of those with recurring hemorrhages. No attempt was made to evaluate the "permanent or five year cures."

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171. Winkelstein, A.; Cornell, A., and Hollander, F.: The Medical Treatment of Peptic Ulcer Refractory to Sippy Therapy, Surgery **17:** 696-704, 1945.

172. Freeman, H.: A Gastroscopic Control of the Treatment of Gastric Ulcer by Duodenal Feeding, Brit. J. Surg. **32:** 303-308, 1944.

173. Ivy, A. C.: The Prevention of Recurrence of "Peptic" Ulcer: An Experimental Study, Gastroenterology **3:** 443-449, 1944.

174. Heuer, G. J.; Holman, C., and Cooper, W. A.: The Treatment of Peptic Ulcer Based upon Ten Years' Experience at the New York Hospital, Philadelphia, J. B. Lippincott Company, 1944, p. 118.

175. Eliason, E. L., and Stevens, L. W.: The Surgical Aspects of Peptic Ulcer, S. Clin. North America **24:**1282-1289, 1944.

As Wangensteen [176] points out, ulcer is essentially the end effect of the digestive action of gastric juice on the gastric or the duodenal wall. It may occur in any one who has a stomach secreting an excessive amount of free hydrochloric acid. Ulcer occurs spontaneously in man but rarely does so in laboratory or domestic animals. Yet, by stimulation of the endogenous mechanism for the secretion of acid, ulcer may be produced almost at will in most of such animals. Under the influence of daily implantation of "histamine in beeswax" a torrent of acid secretion occurs which breaks down the ability of the cells to defend themselves. In consequence of the failure of neutralization of the acid, ulcer comes about. Erosion, which frequently occurs in the stomachs of normal persons, is undoubtedly a common precursor of ulcer. The probability is that the margin of difference between a person who has an ulcer and one who has not is small. Frequent feeding is the essence of a satisfactory conservative management. The long night fast constitutes essentially the most important defect in medical management. The surgical management of ulcer concerns itself primarily with medical failure and with the complications of ulcer. Subtotal gastric resection employing a short afferent duodenal loop is considered the procedure least likely to be complicated by stomal ulcer.[177] Brooks and Meacham,[178] in 57 patients with ulcer with intractable pain, pyloric obstruction and massive hemorrhage, carried out partial gastric resection, with 1 operative death. Of the group, 48 are living and well, 2 have residual symptoms and 1 shows no improvement. Five patients died one to three years postoperatively of conditions entirely irrelevant. The postoperative period of study has varied from one to ten years. Lewisohn [179] contrasts the incidence of jejunal ulcer following gastroenterostomy, 34 per cent, with the recurrence rate of 2.5 to 8 per cent for gastric resection and concludes that subtotal gastrectomy is the surgical treatment of choice for duodenal ulcer. The mortality rate did not exceed 1.5 to 3 per cent. Hinton,[180] on the basis of 85 cases in which he

176. Wangensteen, O. H.: Clinical Aspects of the Ulcer Problem with Special Reference to Definition of the Criteria of a Suitable Operation; the Importance of a Short Afferent Loop, and Results of Operation, Minnesota Med. **27**:714-722, 1944.

177. Wangensteen, O. H.: The Criteria of a Satisfactory Operation for Ulcer and Causes of Failure After Gastric Resection for Ulcer, Minnesota Med. **28**:66-70, 1945.

178. Brooks, B., and Meacham, W. F.: Partial Gastrectomy for Duodenal Ulcer, South. M. J. **38**:150-155, 1945.

179. Lewisohn, R.: Gastric Resection for Duodenal Ulcer, Surg., Gynec. & Obst. **80**:355-360, 1945.

180. Hinton, J. W.: Subtotal Gastrectomy in Medically Resistant Ulcers, New York State J. Med. **45**:291-295, 1945.

operated, covering a two year period, considers intractable pain not responding to intensive and adequate medical therapy to be the indication for surgical intervention, the frequency being about 10 per cent. Subtotal or partial resection with resection of the duodenal ulcer is the operation of choice. Lannin [181] likewise concludes that the most satisfactory procedure is an extensive three-quarter gastric resection including the antrum and employing an efferent loop as short as possible. In 300 patients treated with this procedure, not a single recurrent jejunal ulcer was found. [The reviewers feel constrained to predict, however, that recurrences will develop in time.]

The percentage of patients with duodenal ulcers treated surgically at the Mayo Clinic declined from 38 in 1928 to approximately 13 in 1943, in which year 386 were so treated, with a mortality of 0.8 per cent. There were 157 treated by partial gastrectomy, with a mortality of 0.6 per cent. Of patients with gastric ulcers (145), 65 per cent had partial gastrectomy, with a mortality of 1.4 per cent.[182] At the Massachusetts General Hospital from 1936 through 1943 primary elective subtotal gastrectomy was performed for peptic ulcer three hundred and twenty times, with 12 deaths, a mortality of 3.7 per cent. From 1936 through 1941 resection was performed for gastric ulcer fifty-five times, with no deaths, and resection for duodenal ulcer, one hundred and twenty-four times, with a mortality of 8.1 per cent. Leakage of the duodenal stump seems to have been the major factor in the high mortality. In 1942 and 1943, 51 patients underwent subtotal resection for gastric ulcer, with a mortality of 3.9 per cent. There were no deaths among 94 patients who underwent resection for duodenal ulcer.[183] In Rienhoff's [184] 260 consecutive cases of complicated duodenal ulcer in which the pylorus, the pyloric antrum and a portion of the acid-secreting mucosa of the fundus was resected, the immediate postoperative mortality was 2 per cent; complications developed in 32 per cent, and 66 per cent of the patients remained well. In a group of 79 patients who were treated by subtotal gastrectomy for duodenal ulcer prior to 1937 the mortality was 18.75 per cent. Since that time in 94 patients who were

181. Lannin, B. G.: Experimental Evaluation of a Satisfactory Operation for Ulcer, Surgery **17**:712-741, 1945.

182. Counseller, V. S.; Waugh, J. M., and Clagett, O. T.: Report of Surgery of the Stomach and Duodenum for 1943, Proc. Staff Meet., Mayo Clin. **19**:586-592, 1944.

183. McKittrick, L. S.; Moore, F. D., and Warren, R.: Complications and Mortality in Subtotal Gastrectomy for Duodenal Ulcer: Report on a Two-Stage Procedure, Tr. Am. Surg. A. **62**:531-561, 1944; Ann. Surg. **120**:531-561, 1944.

184. Rienhoff, W. F., Jr.: An Analysis of the Results of the Surgical Treatment of Two Hundred and Sixty Consecutive Cases of Chronic Peptic Ulcer of the Duodenum, Ann. Surg. **121**:583-599, 1945.

treated by gastrectomy the mortality has been 6.25 per cent, according to Colp [185] and his associates. Lahey's[186] impressions are that the incidence of stomal ulcer following gastroenterostomy is 15 per cent; the incidence following subtotal gastrectomy is about 2 to 3 per cent. Gastrojejunal ulcer should be treated medically first; if it is adherent to the transverse colon immediate operation is indicated, to avoid gastrojejunocolic fistula. Lahey does not advise that the Finsterer method of exclusion be followed because in 20 instances of such resection he observed the highest incidence of jejunal ulcer. The mortality from subtotal resection for ulcer should not be over 3 per cent. In 318 consecutive cases in which subtotal gastrectomy was done for ulcer 62 of the lesions were in the jejunum, 56 developed after gastroenterostomy and 6 after previous subtotal resection. The mortality from resection for gastric and duodenal ulcer was 2.8 per cent; that from resection for jejunal ulcer, 4.8 per cent.

A new and different surgical approach to the treatment of peptic ulcer has been suggested by Dragstedt,[187] i. e., supraphrenic bilateral vagotomy. In 10 cases of duodenal ulcer and 1 of gastric ulcer in which this procedure was tried the operation was well tolerated, although in 1 case postoperative nonfatal pneumonia occurred. The continuous night secretion in most of the patients before operation was abundant; in 7 it exceeded a liter in twelve hours. After the operation this secretion decreased 50 per cent in all patients. The number of patients subjected to this procedure has increased to approximately 100,[188] with 1 fatality (postoperative pneumonia) and with no known recurrence of ulcer to date.

In a subsequent report it is noted that 3 patients required gastroenterostomy because of persistence of symptoms of obstruction. These results suggest to the authors that gastroduodenal ulcer is a psychosomatic disease in which the central nervous system affects the stomach "via the vagi," probably chiefly through the greatly augmented secretion of gastric juice.[189] Apparently, little diminution of the nervous phase of gastric secretion is to be expected from partial vagotomy, and of course the chemical secretory phases are entirely unaffected.

185. Colp, R.; Klingenstein, P.; Mage, S., and Druckerman, L. J.: Subtotal Gastrectomy for Duodenal Ulcer, Ann. Surg. **120**:170-180, 1944.

186. Lahey, F. H.: Inflammatory Lesions of the Stomach and Duodenum, J. A. M. A. **127**:1030-1036 (April 21) 1945.

187. Dragstedt, L. R.; Palmer, W. L.; Schafer, P. W., and Hodges, P. C.: Supra-Diaphragmatic Section of the Vagus Nerves in the Treatment of Duodenal and Gastric Ulcers, Gastroenterology **3**:450-462, 1944.

188. Dragstedt, L. R.: Personal communication to the authors.

189. Dragstedt, L., and Schafer, P. W.: Removal of the Vagus Innervation of the Stomach in Gastroduodenal Ulcer, Surgery **17**:742-749, 1945.

The insulin test in the hands of Weinstein and his associates [190] proved to be an unfailing means of determining the persistence of part of the gastric vagus supply. In 6 clinical cases the condition was apparently not improved by partial vagotomy.

(*i*) Benign and Malignant Ulcer: Allen [191] in a ten year experience found that 14 per cent of the lesions treated as benign gastric ulcer proved to be cancer. Wiley [192] estimates that in 10 per cent of the cases the differentiation cannot be made.

(*j*) Massive Hemorrhage: Clark [193] discusses 112 patients with gross bleeding from the upper part of the digestive tract whom he encountered over a period of twenty years. In 94 of these the hemorrhage was attributed to ulcer, duodenal in 86 and gastric in 8. It is interesting that, of 1,254 patients with a history of ulcer whom he encountered in private practice, only 94 had had massive hemorrhage. Tidmarsh [194] recommends immediate and frequent feedings; barbiturates are preferable to opium. With continued and repeated bleeding, particularly when accompanied by arteriosclerosis, early surgical intervention should be considered.

Wakim and Mason [195] in an experimental study on trained dogs found that hemorrhage in amounts of approximately 25 per cent of the estimated total blood volume led to immediate cessation of intestinal activity and that recovery immediately followed replacement of the withdrawn blood or reinjection of the cells suspended in a quantity of Ringer's solution equivalent to the volume of the discarded plasma. The depletion of plasma proteins caused by repeated plasmapheresis also decreased intestinal activity, with a delay in the appearance of the feeding reaction.

Gregory, Ewing and Levine [196] observed that a drop in the systolic blood pressure to 70 or 80 mm. of mercury resulted in a rise of blood urea nitrogen to 25 mg. per hundred cubic centimeters. Blood given by

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190. Weinstein, V. A.; Colp, R.; Hollander, F., and Jemerin, E. E.: Vagotomy in the Therapy of Peptic Ulcer, Surg., Gynec. & Obst. **79**:297-305, 1944.

191. Allen, A. W.: Gastric Ulcer and Cancer, Surgery **17**:750-754, 1945.

192. Wiley, H. M.: Gastric Ulcer, Benign or Malignant: A Review of Recent Literature, Am. J. Surg. **65**:104-111, 1944.

193. Clark, W. E.: The Significance and Management of Massive Bleeding from the Upper Gastro-Intestinal Tract, South. M. J. **38**:24-30, 1945.

194. Tidmarsh, C. J.: Medical Treatment of Ulcer Hemorrhage, Canad. M. A. J. **52**:21-24, 1945.

195. Wakim, K. G., and Mason, J. W.: The Influence of Hemorrhage and of Depletion of Plasma Proteins on Intestinal Activity, Gastroenterology **4**:92-101, 1945.

196. Gregory, R.; Ewing, P. L., and Levine, H.: Azotemia Associated with Gastrointestinal Hemorrhage, Arch. Int. Med. **75**:381-394 (June) 1945.

stomach tube raised the blood urea nitrogen level to 25 to 50 mg. per hundred cubic centimeters. The variations in the blood urea nitrogen due to ingestion of blood occurred more rapidly than the ones due to lowering of the blood pressure. Severe anemia did not cause azotemia. The combined effects of lowering the blood pressure and giving blood by stomach tube produced higher levels than would be expected from either alone. Azotemia may be due to decreased renal function caused by low blood pressure, dehydration and absorption of digested blood proteins; anemia is not a factor.

Levy [197] reports on 11 patients who were suffering severe hemorrhage and who were treated with the usual Sippy diet, to which was added a daily oral intake of from 100 to 200 Gm. of mixed amino acids. The serum protein returned to normal in an average of ten and two-tenths days. In a control group of 6 patients given the same diet without the amino acids the serum protein returned to normal in an average of nineteen days.

(*k*) Jejunal Ulcer: Morlock and Walters [198] describe three interesting jejunal ulcers attached to and burrowing deeply into the anterior abdominal wall. Sarason [199] reports the successful treatment of a recurrent gastrojejunocolic fistula.

(*l*) Perforation: Graham and Tovee [200] report a mortality of 6.3 per cent in a series of 114 cases of perforated duodenal ulcer. Bacterial peritonitis is a late manifestation, since, of 59 cultures, 34 were sterile; in only 2 cases were colon bacilli obtained. Bisgard [201] found that subtotal gastric resection could be performed in the presence of diffuse soiling of the peritoneal cavity within twelve hours after the perforation of an ulcerating lesion of the stomach, the duodenum or the jejunum in patients in good condition, with a mortality lower than that observed in patients treated by simple closure with sutures.

Under the heading of noncancerous duodenocolonic fistula McClinton [202] describes a case thought to be the fifth in the literature since

197. Levy, J. S.: The Effect of Oral Administration of "Amino Acids" on the Hypoproteinemia Resulting from Bleeding Peptic Ulcer: Preliminary Report, Gastroenterology **4**:375-387, 1945.

198. Morlock, C. G., and Walters, W.: Peptic Ulcer Perforating into the Anterior Abdominal Wall, Am. J. Surg. **65**:133-137, 1944.

199. Sarason, E. L.: Recurrent Gastrojejunocolic Fistula, J. Mt. Sinai Hosp. **11**:282-285, 1945.

200. Graham, R. R., and Tovee, E. B.: The Treatment of Perforated Duodenal Ulcers, Surgery **17**:704-712, 1945.

201. Bisgard, J. D.: Gastric Resection for Certain Acute Perforated Lesions of Stomach and Duodenum with Diffuse Soiling of the Peritoneal Cavity, Surgery **17**:498-509, 1945.

202. McClinton, J. B.: Non-Malignant Duodeno-Colonic Fistula, Canad. M. A. J. **51**:434-436, 1944.

1885; in all the fistula followed rupture of a duodenal ulcer without operation. The report contains these interesting sentences:

> The effect of stomach secretions on the colon was baffling. It appeared that hydrochloric acid trickling down was irritating to the colon.
>
> On the writer's suggestion, Dr. D. W. Gordon Murray, of the Toronto General Hospital, conducted experiments on colostomy cases by injecting dilute hydrochloric acid. He states as follows:
>
> "Since your suggestion regarding the effect of hydrochloric acid on the colon, I have had four colostomies in whom we tried injecting a dilute solution of HCl. It is my impression from this experience, that the HCl produces hyperperistalsis with secretion of mucus. In two, after going on for ten days or more, there was some blood in the mucus suggesting a rather active colitis as a result of the acid."

(*m*) Ulcer in Infancy and Childhood: Donovan and Santulli [203] report 10 cases of peptic ulcer encountered at the Babies Hospital of New York in the period from 1930 to 1944 and suggest that the diagnosis probably would be made more frequently if it were realized that the condition occurs in this age group. Hemorrhage was present in 6 of the 10 children. Perforation and pyloric stenosis also were observed.

Florer and Ochsner [204] observed a traumatic chylothorax complicated by fatal perforation of a duodenal ulcer in a 14 year old boy.

(*n*) Ulcer in Men in Military Service: Zetzel [205] in an army station hospital found that, of 21,856 patients admitted in one year, 1,802 (8.1 per cent) were sent to the gastrointestinal section. Duodenal ulcer was found in 125 of these and gastric ulcer in 5, making an incidence of peptic ulcer of 7.2 per cent. Perforation and hemorrhage occurred in 6 of each group. Among 22,000 patients admitted over a two year period in a general hospital in Panama there were 66 (0.3 per cent) who had peptic ulcer, and 10 of these were suffering from acute perforations; there were no deaths. There was no seasonal incidence.[206] Among 1,702 patients with abdominal symptoms Loder and Kornblum [207] found only 82 with duodenal and none with gastric ulcers. The incidence was the same in white and colored patients. The percentages of peptic ulcer, acute and chronic gastritis and bacillary dysentery were

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203. Donovan, E. J., and Santulli, T. V.: Gastric and Duodenal Ulcers in Infancy and in Childhood, Am. J. Dis. Child. **69**:176-179 (March) 1945.

204. Florer, R., and Ochsner, A.: Traumatic Chylothorax: Report of a Fatal Case Complicated by a Ruptured Duodenal Ulcer, Surgery **17**:622-629, 1945.

205. Zetzel, L.: Experiences with Peptic Ulcer in an Army Station Hospital, Gastroenterology **3**:472-479, 1944.

206. Harrell, W. B., and Wilson, R. O.: Ruptured Peptic Ulcer Among United States Troops in Panama, Mil. Surgeon **96**:336-342, 1945.

207. Loder, H. B., and Kornblum, S. A.: Duodenal Ulcer in a Large Army Camp: Incidence and Statistical Analysis, Mil. Surgeon **96**:492-497, 1945.

practically identical in colored and white patients admitted to a large army hospital.[208]

Feasby[209] estimates that in the rapid clinical examinations of Canadian recruits for duodenal ulcer a 12 per cent error was made. In half of the 12 per cent ulcer was diagnosed but not confirmed; in the other half it was found when not expected. With regard to the usefulness of patients with ulcer, Feasby reports that "only 10 per cent of a selected group of men with healed ulcer were able to carry on indefinitely after return to duty, either in England or in Canada." Hook and Keane[210] in studying 306 Navy-enlisted men with duodenal ulcer found that 2 of 3 had had their symptoms prior to enlistment; there was no evidence to justify the belief that military service is conducive to the production of ulcer. Of the total group, 40.5 per cent were discharged, the others were sent to limited service and some were returned to regular duty.

Berk and Frediani[211] interpret the prevalence of peptic ulcer in the Army as largely a reflection of its unsuspected frequency in the adult civilian population. The psychosomatic aspects, the influence of anxiety, tension and emotional unrest, seem to him unmistakable. Somewhat in accord with this view is an experiment in the rehabilitation of 100 soldiers with dyspepsia in which satisfactory results were obtained in 38 per cent of the 50 patients with peptic ulcer and in 70 per cent of the group as a whole. In the patients who did poorly, the factor of poor morale seemed to have been important. These studies confirmed those of Rook, who found that the higher the grade, the greater the percentage of men who could be salvaged—"only those who want to stay in the service will make a real attempt to regulate their life so that they can carry on."[212] The incidence of peptic ulcer in 289 hospitalized dyspeptic patients was 34 per cent; the incidence in 682 outpatients was only 11 per cent. "Definite psychiatric factors were present in less than 25 per cent of the patients with ulcer and in less than 50 per cent of

208. Kirchner, A. A.: The Digestive Disturbances of the Negro Soldier as Seen in a Large Army General Hospital, Rev. Gastroenterol. **11**:397-408, 1944.

209. Feasby, W. R.: Peptic Ulcer in the Canadian Army (1940 to 1944), War Med. **6**:300-303 (Nov.) 1944.

210. Hook, F. R., and Keane, R. H.: The Plight of the Ulcer Patient in Military Service: Study of Three Hundred and Six Enlisted Personnel with Duodenal Ulcer, U. S. Nav. M. Bull. **44**:519-529, 1945.

211. Berk, J. E., and Frediani, A. W.: The Peptic Ulcer Problem in the Army, Gastroenterology **3**:435-442, 1944.

212. Rook, A. F.: Peptic Ulcer: Prognosis in Royal Air Force Patients, Lancet **1**:733-736, 1943; cited by Goldbloom, A. A., and Schildkrout, H.: Dyspepsia Regimen: A Method of Rehabilitation, War Med. **6**:24-26 (July) 1944.

those without ulcers." "Rehabilitation of the dyspeptic soldier presupposes a high standard of morale, a definite desire to serve the army and a lesion which can respond to appropriate medical and dietary management." [While the reviewers are in complete accord with the view that the personality of the patient is of great importance in the management of peptic ulcer, just as it is indeed in almost all chronic diseases or disorders, nevertheless it is premature to conclude that ulcer is a "psychosomatic disease." [213]] Reference may be made to the excellent discussion of this subject by Kirk, which was briefly summarized last year.[214]

A liberal convalescence diet was used, with no medicament except an occasional alkaline powder for symptomatic relief, in 478 patients with peptic ulcer admitted to the Hammond General Hospital. Clinical cures were obtained in 438. Thirty-seven patients not relieved were given a special diet containing bland foods, raw eggs, large amounts of butter, fresh greens and olive oil, which is considered to be rich in an antiulcer factor. Complete relief was obtained in 34 of the 37. [The results obtained seem to the reviewers to be those to be expected during hospitalization on almost any type of medical program and hence do not prove either the superiority of this regimen or the validity of the "vitamin A hypothesis." [215]] Baumgartner [216] advocates the use of the original Sippy program.

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213. Schildkrout, H.: Management of the Dyspeptic Soldier in a Staging Area. War Med. **6**:151-157 (Sept.) 1944.

214. Kirk, R. C.: Peptic Ulcer at Fort Sill, Am. J. Digest. Dis. **10**:411-413. 1943.

215. Gianelli, V. J., and Bellafiore, V.: The Fundamental Importance of Diet in the Treatment of Peptic Ulcer in an Army General Hospital, M. Clin. North America **29**:706-713, 1945.

216. Baumgartner, M. M.: Peptic Ulcer in Naval Personnel, U. S. Nav. M. Bull. **44**:995-999, 1945.

(To Be Concluded)

Book Reviews

Structure and Function of the Human Body. By Ralph N. Baillif, Ph.D., and Donald L. Kimmel, Ph.D. Price, $3. Pp. 328, with 286 illustrations. Philadelphia, London and Montreal: J. B. Lippincott Company, 1945.

This book presents anatomy and physiology in a concise and interesting form. The authors have retained all of the material necessary for the understanding of the basic course in anatomy and physiology. The great mass of details which often confuses the beginner has been eliminated. Such details could be added as supplemental material for lectures, if desired by the instructor.

The long introductory unit is so planned that it gives the student a comprehensive view of the entire anatomic field and the relationships involved. This unit is written with a minimum use of scientific terms and ends with an introduction to scientific terms. The glossary at the end of the book is one of its outstanding features.

Unit 2 is divided into discussions of the skeletal, muscular and circulatory systems. The drawings in this unit are particularly clear and form an excellent adjunct to the text.

Unit 3 deals with the digestive and respiratory systems, and unit 4, with the urogenital, endocrine and nervous systems. In both of these units the anatomy and physiology are so clearly presented and so closely correlated that the beginning student should have no difficulty in integrating structure and function. Drawings again help to enhance the explanations presented in the text.

The chapters are so planned that, although they have been grouped into units, the grouping is arbitrary and the method of presentation can be varied without loss of continuity in subject matter.

The only adverse criticism which might be presented, and this is a minor one, is that the book does not contain enough material to warrant its use as a text if only one course of anatomy and physiology is taught. It is a very good text for the initial presentation of the subject or for use as a review text.

Fitografia alergolica. By Jose Martorelli. Price unknown. Pp. 195. Buenos Aires, Argentina: Libería y editorial "El Ateneo," 1945.

This is a monograph dealing with the plants and pollens causing hay fever in the state of Cordova in Argentina. The introductory chapter gives a short botanical review of pollen and the process and functions of pollination. The third chapter deals with distribution of vegetation in Cordova. The fourth and fifth chapters describe the forms and structure of pollen, the methods of collecting pollen, the counting of pollen and several anemopollinometers, of complicated design. Chapter 6 constitutes half of the volume of the monograph and contains the most important feature of the book. It is a complete study of plants and pollens in Rio Cuarto and southeast Cordova. Included are many fine photographs of plants in their natural habitat and as dried specimens. There are also a large number of photographs of pollens. A pollination calendar gives valuable data. The most important hay fever season comprises the months of February and March, when the chenopods and amaranths pollinate. The grasses pollinate from November to May but do not produce large quantities of pollen.

This monograph is a valuable contribution to the knowledge of hay fever in South America. It should be of interest to allergists in the United States, physicians in Argentina and all those who will be called on to advise allergic globe trotters in their future travels.

Diagnostik und Therapie der Magen- Darmerkrankungen in Zwölf Vorlesungen (Diagnosis and Treatment of Gastrointestinal Diseases, in Twelve Lectures). By Fritz Hirschberg, M.D. Price, 30 Danish crowns. Pp. 352, with 110 illustrations. Copenhagen, Denmark: Einar Munksgaard, 1941.

This beautifully printed volume presents a series of informal yet polished lectures on the diagnosis and treatment of disorders of the stomach, small intestine, colon and rectum. The emphasis is on diagnosis, and there are many useful hints on the taking of histories, the physical examination and the interpretation of roentgenograms; in addition there is much that is instructive regarding the treatment of peptic ulcer, colitis and tumors, whether medical or surgical.

If the book has a defect, the defect is one which is shared with most medical literature of the present time and which ought to be outgrown in the near future, namely, a lack of appreciation of what medical statistics (in the best sense of the word) has to offer. An abundance of quantitative information is now becoming available from operations and necropsies and would often permit much more exact statements as to the relative frequencies of various complaints, the distribution of ulcers over the inner surface of the stomach, the probability that a given subjective complaint is accompanied with a particular organic change and so on. While much of this can be stated in percentages and does not presuppose more than sixth grade arithmetical achievements on the part of the reader, there lies beyond this the field of combinations, permutations and probability, familiar to students of first year algebra. With the help of these concepts it would often be possible to make much more definite statements regarding associations of symptoms and effects of treatment.

The author is to be commended for introducing on page 36 Forssell's nomenclature of the parts of the stomach. The wider use of this nomenclature would save anatomists the necessity of explaining, year after year, why the top of the stomach is called the bottom (fundus). This part is called the fornix in Forssell's system, which is much better adapted to the roentgenographic appearance of the living stomach in the erect subject.

The two outstanding features of the book are its numerous roentgenographic illustrations and its readable, unaffected style. It should be inspiring and useful to any one interested in either the medical or the surgical aspects of gastrointestinal disease and deserves a translation into English.

Pulmonary Edema and Inflammation; an Analysis of Processes Involved in the Formation and Removal of Pulmonary Transudates and Exudates. Monographs in Medicine and Public Health, Number 7. By C. K. Drinker, M.D. Price, $2.50. Pp. 106, with 27 illustrations. Cambridge, Mass.: Harvard University Press, 1945.

In this monograph Drinker has combined the studies that have been made by him and his associates at Harvard on the physiologic mechanisms and pathologic changes that are responsible for the functioning of the lung in the first place and in the second place for the production of disease. His own investigations he has correlated with the researches of others to produce a book which should be of inestimable value to the clinician. Edema of the lungs is a very common medical emergency with which the physician should be thoroughly acquainted, not only with how it is produced but also with how to combat it.

Lastly, Drinker discusses the problems of artificial respiration and reviews the various technics employed in maintaining artificial respiration. Cessation of respiration is an important, often dramatic and frequently catastrophic accident in medicine with which all physicians should be thoroughly familiar. The book is authoritative, practical and scientific.

Los Problemas del Cardiaco. By J. M. Hoyos, M.D. Price unknown. Pp. 153. México, D. F.: Revista de Medicina y Ciencias Afines, 1945.

Dr. Meneses Hoyos wrote this book with a single purpose: to disentangle the patient with cardiac disease from the web of prejudices and legends in which he lives, which perhaps contribute as much as the disease itself to the undermining of his spiritual strength and to the embitterment of his life. The book was written primarily for the general practitioner; yet its simple, clear, concise style will appeal as well to the specialist, the student and even the layman interested in medical literature.

Each chapter discusses a common and erroneous concept of heart disease without minimizing the germ of truth behind it. Nevertheless, fallacies are pointed out sharply in a simple and understandable manner through the judicious use of technical information.

The book begins with a discussion of the factors of inheritance in heart disease. This is followed by a section on prognosis of the cardiopathies, with emphasis on the fact that a useful, creative life need not be contraindicated in many of them. The efficiency of the circulatory mechanism at various altitudes is discussed, and the physiologic data are correlated with specific information regarding the effects of changes in atmospheric pressure on the diseased heart.

The dietary problem in cardiac disease is presented, with a simple explanation of the fundamental principles behind it. The chapters on tobacco and alcohol are sound discussions of their relation to the pathology of the heart. A section is dedicated to the work capacity of the diseased heart, in which Dr. Meneses Hoyos gives emphasis to the individual differences of each case and clarifies the fallacy of complete invalidism in all types of cardiac disease. The chapter on the problem of pregnancy in the woman with cardiac disease is followed by discussions of the risk of surgical intervention, of sudden death from cardiac disease and of arteriosclerosis and allied degenerative processes. In the final chapter the author presents his recommendations for the prevention of the cardiopathies as an individual and social proplem.

To illustrate his discussions, Dr. Meneses Hoyos has drawn extensively on his own medical experience. The effectiveness of the presentation of the subject owes much to the clinical studies of cases which are summarized throughout the book.

Clinical Roentgenology of the Heart. By J. B. Schwedel, M.D. Annals of Roentgenology, Volume 18. Price, $12.50. Pp. 400, with 732 illustrations. New York: Paul B. Hoeber, Inc., 1945.

There are many illustrations and diagrams in this new book, which present the problem of clinical roentgenography of the heart in the usual fashion. There is nothing particularly different in this presentation from that in other monographs or books already available. A correlation is made of the clinical, pathologic and roentgenographic data, but this is marred by either carelessness or the presentation of noncorrelating data. For example, on pages 64, 90 and 128 the electrocardiograms are improperly mounted (lead III of figure 36 *C* is upside down and reversed; essentially the same holds for those of figure 53 *J* and figure 72 *C*). Many illustrations are not very clear, e. g., figures 53 *L*, 119 *D*, 95 *C*, 93 *A*, 131 *B*, 73 *A* and 73 *C*. Fewer but better illustrations would make the book of greater value for the beginner than it can be now. The reader who is fairly well informed can recognize the errors and can profit somewhat from the book anyway.

The author unnecessarily brings in too many purely clinical statements based mainly on opinion. He states on page 129 that the diagnosis of failure of the right side of the heart is "confirmed by demonstration of enlargement of the right ventricular inflow tract" and, "The use of digitalis and diuretics provides only a poor or a temporary remission; the dyspnea and cyanosis are relieved by oxygen. Death usually follows bronchopneumonia or coma." These are among the remarks concerning chronic failure of the right side of the heart. Obviously, they are of

relatively little roentgenographic importance or are of questionable validity in many individual circumstances. The section on cardiology is relatively inadequate and adds little to the book. This is particularly true of the superficial remarks on therapy. It is difficult to recommend this book highly.

Preventive Medicine and Public Health. By Wilson G. Smillie, M.D. Price, $6. Pp. 607. New York: The Macmillan Company, 1946.

The reviewer knows of no one better qualified to write a book on preventive medicine and public health than Dr. Smillie. When one glances through the 600 odd closely printed pages, one realizes how large the subject has become. Naturally, there is some overlapping with what one finds in texts on bacteriology, infectious diseases and nutrition, but this can hardly be avoided. The sections on general matters, such as vital statistics and sanitation, are especially well done. On the whole the book is useful both for reference and for a survey of the whole subject.

News and Comment

WINNER OF 1946 CASH PRIZE AWARD OF NATIONAL GASTROENTEROLOGICAL ASSOCIATION

The winning contestant of the $100 prize offered by the National Gastroenterological Association for the best unpublished manuscript on gastroenterology or an allied subject is Capt. Irving B. Brick, Medical Corps, Army of the United States, for his paper, "Radiation Effects on the Human Stomach: A Preliminary Report." The check was presented to Captain Brick at the annual banquet of the association, held at the Hotel Pennsylvania on Thursday evening, June 20, 1946.

Certificates of merit were awarded to Dr. Frank L. Apperly, Richmond, Va.; Dr. William Nimeh, México, D. F., Mexico, and Dr. Juan Nasio, Rosario, Argentina.

The winning paper, as well as the papers by physicians who received certificates of merit, will be published in the *Review of Gastroenterology*.

ANNUAL SESSION OF AMERICAN COLLEGE OF PHYSICIANS

The twenty-eighth annual session of the American College of Physicians will be held in Chicago, April 28 through May 2, 1947. The officers are: Dr. David P. Barr, New York, president; Dr. LeRoy H. Sloan, Chicago, general chairman, and Mr. Edward R. Loveland, executive secretary, 4200 Pine Street, Philadelphia 4.